(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 049 728
A2

AP

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 81108368.8

(22) Date of filing: 19.01.81

(51) Int Cl.³ A 23 K 1/16
A 23 L 1/31, C 07 C 91/40

(30) Priority: 25.08.80 US 181254
25.08.80 US 181255

(43) Date of publication of application:
21.04.82 Bulletin 82/16

(84) Designated Contracting States:
BE CH DE FR GB IT LI NL SE

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(54) Phenylethane derivatives and acid addition salts thereof for enhancing the growth rate of meat-producing animals, improving the efficiency of feed utilization thereby and/or improving the lean meat to fat ratio thereof.

(57) There is provided a method for enhancing the growth rate of meat-producing animals, improving the efficiency of feed utilization thereby, and or improving the lean meat to fat ratio thereof, which involves, orally or parenterally, administering to said animals a growth-enhancing amount of a phenylethane compound or the acid addition salt thereof.

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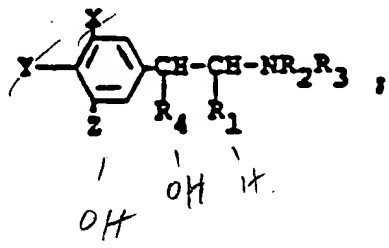
PHENYLETHANE DERIVATIVES AND ACID ADDITION SALT THEREOF FOR ENHANCING THE GROWTH RATE OF MEAT-PRODUCING ANIMALS, IMPROVING THE EFFICIENCY OF FEED UTILIZATION THEREBY AND/OR IMPROVING THE LEAN MEAT TO FAT RATIO THEREOF

SUMMARY OF THE INVENTION

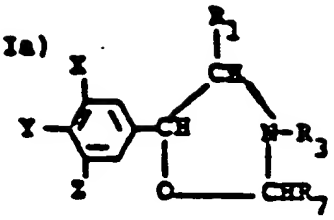
Substitution products of 1-(amino-dihalophenyl)-2-aminoethanes, and the acid addition salts thereof, are disclosed in United States Patent 3,536,712, issued October 27, 1970. Specifically, methods for the synthesis of said compounds are disclosed as useful for enhancing the blood circulation, and as bronchodilators, analgesics, sedatives, antipyretics, antiphlogistics and antitussives in warm-blooded animals. However, only the analgesic utility is examplified. The preparation of other related 1-(amino-dihalophenyl)-2-aminoethanols and their derivatives are disclosed in Japanese Kokai 77 83,619 (Chemical Abstracts, 87,201061r), German Offenlegungsschrift 2,804,625 (1979), German Offenlegungsschrift 2,157,040 (1973), German Offenlegungsshrift 2,261,914 (1974), Europen Patent Application 8,715 (1980), Netherlands Patent Application 7,303,612 (1973). These applications

disclose uses selected from analgesics, broncholytic, antiinflammatory, uterine spasmolytic, β-blocking activities, antispasmolytic activity on cross-striped muscle structure, for tocology, reducing blood pressure by peripheral vasodilation and mobilizing body fat, and for treating allergies. There is no indication or suggestion in any of these disclosures that said compounds are effective as growth-promoting agents for meat-producing animals, such as poultry, cattle, sheep or the like; nor is there any suggestion that said compounds improve the efficiency of feed utilization by said meat-producing animals.

In accordance with the process of the invention, it has been found that the growth rate of meat-producing animals such as chickens, turkeys, rabbits, sheep, swine, goats and cattle, including calves, can be increased, the efficiency of feed utilization thereby measurably improved, and the lean meat to fat ratio improved by the oral or parenteral administration to said animals of an effective amount of a compound selected from the group consisting of:

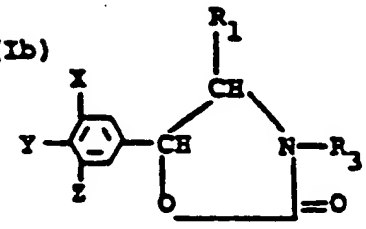
(I) 

(Ia)



; and

(Ib)



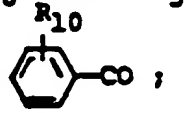
wherein, X is hydrogen, halogen or -CN;

Y is hydrogen, NR_8R_9 or $NHCOR_5$;

Z is hydrogen, halogen, OH, CN, CF_3, $COOR_1$, $CONH_2$, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2, C_1-C_4-dialkylaminomethyl or hydroxymethyl;

R_1 is hydrogen or C_1-C_4 alkyl;

R_2 is hydrogen, C_1-C_6 alkyl, C_3-C_4 alkenyl, C_2-C_5 alkanoyl or

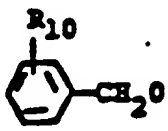


;

R_3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, methoxypropyl, C_3-C_4 alkenyl, phenyl, 2-hydroxyethyl, α,α-dimethylphenethyl, benzyl, 3-phenylpropyl or 3-(4-carbomethoxyphenyl)propyl; and when R_2 and R_3 are taken together with the nitrogen to which they are attached, they represent morpholino or N'-C_1-C_4 alkylpiperazino;

R_4 is hydrogen, OH, OR_6 or SR_{11};

R_5 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy,



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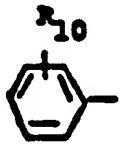
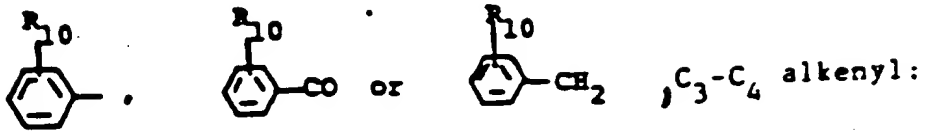


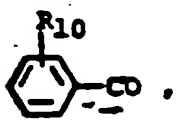
or $N(R_1)_2$;

R_6 is C_1-C_6 alkyl, C_2-C_5 alkanoyl,



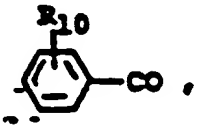
, C_3-C_4 alkenyl:

R_7 is hydrogen, C_1-C_4 alkyl or phenyl;
R_8 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkenyl;
R_9 is hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_3-C_4 alkenyl, or benzyl; and when R_8 and R_9 are taken together with the nitrogen to which they are attached, they represent pyrrolidino; R_{10} is chloro, dichloro, methyl, dimethyl, methoxy, dimethoxy or nitro; R_{11} is C_1-C_6 alkyl, phenyl or benzyl; with the provisos that when R_3 is phenyl, 2-hydroxyethyl, α,α-dimethylphenethyl, C_3-C_6 cycloalkyl, benzyl, methoxypropyl, 3-phenylpropyl, or 3-(4-carbomethoxyphenyl)propyl, R_2 is hydrogen; and when R_3 is hydroxyethyl, R_4 is hydroxyl and the compound is (I); and when R_6 is alkanoyl or



,

R_2 and R_3 are substituents other than hydrogen, except when R_3 is an alkyl or substituted alkyl group which contains a tertiary carbon attached to nitrogen; and when Y is hydrogen, X and Z are halogen, and R_2 is hydrogen, C_3-C_5 alkanoyl or



,

R_3 is isopropyl, 2-butyl, or t-butyl; and when R_8 is C_1-C_4 alkyl or C_3-C_4 alkenyl, R_9 is hydrogen.

C_1-C_4 alkyl or C_3-C_4 alkenyl; and when Z is OH, X and Y are hydrogen; and that at least one of X, Y, and Z represents a substituent other than hydrogen; and when X is -CN, Z is -CN; and when Z is hydroxymethyl, R_4 is OH; and when Z is a group other than halogen, Y is NR_8R_9 or $NHCOR_5$; and when R_5 is $N(R_1)_2$, R_4 is OH; and further provided that when X is hydrogen or halogen, and Y is hydrogen, NH_2 or $NHCOR_5$, and Z is hydrogen, halogen or OH, then R_4 cannot be hydrogen, OH or OR_6 where R_6 is C_1-C_6 alkyl; racemix mixtures of the above - identified compounds and the optically active isomers, and non-toxic, pharmacologically acceptable acid addition salts thereof.

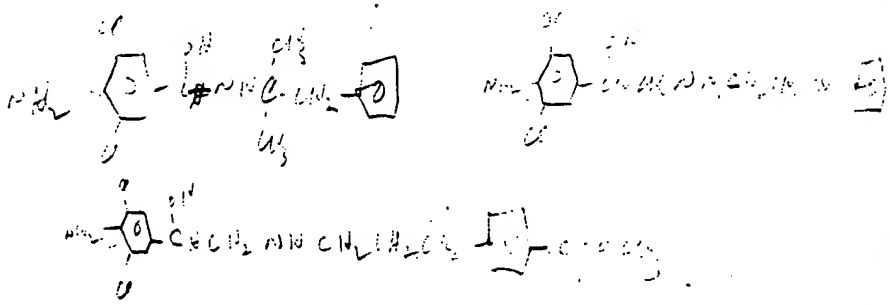
A preferred group of compounds for use in the method of this invention have the above formula I structure wherein X is hydrogen or halogen; Y is hydrogen, NR_8R_9 or $NHCOR_5$; Z is halogen, OH, CN, CF_3, $COOR_1$, $CONH_2$, methyl, methoxy, NO_2, C_1-C_4 dialkylaminomethyl, or hydroxymethyl; and the remaining groups are as hereinbefore defined; or a non-toxic, pharmacologically acceptable acid addition salt thereof.

Another preferred group of compounds for use in the method of this invention have the above formula I structure wherein X is hydrogen, chlorine, or bromine; Y is hydrogen or NR_8R_9; Z is chlorine, bromine, CN, CF_3; R_1 is hydrogen or methyl; R_4 is OH, OR_6, SR_{11}; R_6 is C_1-C_6 alkyl, benzyl, C_2-C_5 alkanoyl, or benzoyl; or a non-toxic, pharmacologically acceptable acid addition salt thereof.

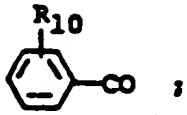
The most preferred compounds for use in this invention are: 4-amino-N-tert-butyl-3,5-dichloro-α-methoxyphenethylamine; N-tert-butyl-

3,5-dichloro-β-methoxy-4-methylaminophenethylamine; α-[(tert-butylamino)methyl]-3,5-dichloro-4-isopropylaminobenzyl alcohol; 5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile; 5-[2-(tert-butylamino)-1-hydroxyethyl]anthranilonitrile; methyl-5-[2-(tert-butylamino)-1-hydroxyethyl)-3-chloroanthranilate; 4^1-[2-tert-butylamino)-1-hydroxyethyl]-2^1,6^1-dichlorovaleranilide; benzyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocarbanilate; 5-acetylanthranilonitrile; 4-amino-N-tert-butyl-3,5-dichloro-β-(methylthio)phenethylamine; N-tert-butyl-3,5-dichloro-β-methoxyphenethylamine; α-[(tert-butylamino)-methyl]-3,5-dichloro-4-methylaminobenzyl alcohol; α-[(tert-butylamino)methyl-3,5-dichloro-4-dimethylaminobenzyl alcohol; 4-amino-3,5-dichloro-α-{[(3-phenylpropyl)amino]methyl}benzyl alcohol; 4-amino-3,5-dichloro-α-{[α,α-dimethylphenethyl)amino]methyl}benzyl alcohol; 4-amino-N-tert-butyl-3,5-dichloro-β-ethoxyphenethylamine; methyl-p-{3-[(4-amino-3,5-dichloro-β-hydroxyphenethyl)amino]propyl}benzoate; methyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocarbanilate; 4^1-[2-(tert-butylamino)-1-hydroxyethyl]-2^1,6^1-dichloroacetanilide; 5-[2(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile; 4-amino-β-(benzyloxy)-N-tert-butyl-3,5-dichlorophenethylamine and the non-toxic, pharmaceutically acceptable acid addition salts thereof.

Although it is evident from the above discussion that certain compounds represented by formula I above are described in the literature, many compounds represented by formula I are new and unobvious. The novel and unobvious compounds of the present invention are represented by the structure of formula I,

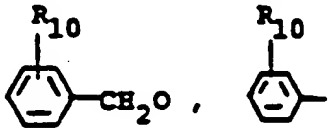


wherein X is hydrogen, halogen or -CN;
Y is hydrogen, NR_8R_9 or $NHCOR_5$;
Z is halogen, -CN, CF_3, $COOR_1$, $CONH_2$, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2 or C_1-C_4 dialkylaminomethyl;
R_1 is hydrogen or C_1-C_4 alkyl;
R_2 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_4 alkenyl, C_2-C_5 alkanoyl or



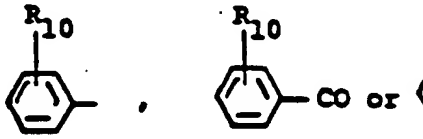
;

R_3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_4 alkenyl, phenyl or benzyl;
R_4 is OH, OR_6 or SR_{11};
R_5 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy,



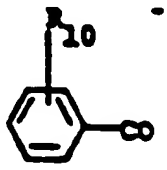
or $N(R_1)_2$;

R_6 is C_1-C_6 alkyl, C_2-C_5 alkanoyl,

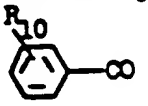


;

R_8 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkenyl;
R_9 is hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_3-C_4 alkenyl, or benzyl; R_{10} is hydrogen, chloro, dichloro, methyl, dimethyl, methoxy, dimethoxy or nitro;
R_{11} is C_1-C_6 alkyl, phenyl, benzyl; with the provisos that when Y is NH_2 , $NHCH_3$, NHC_2H_5 or $NHCOR_5$, R_4 is OR_6 or SR_{11}; and when Y is hydrogen, X and Y are halogen, R_2 is hydrogen, C_2-C_5 alkanoyl or



and R_3 is isopropyl, 2-butyl or t-butyl; and when X is -CN, Z is -CN; and when R_6 is alkanoyl or

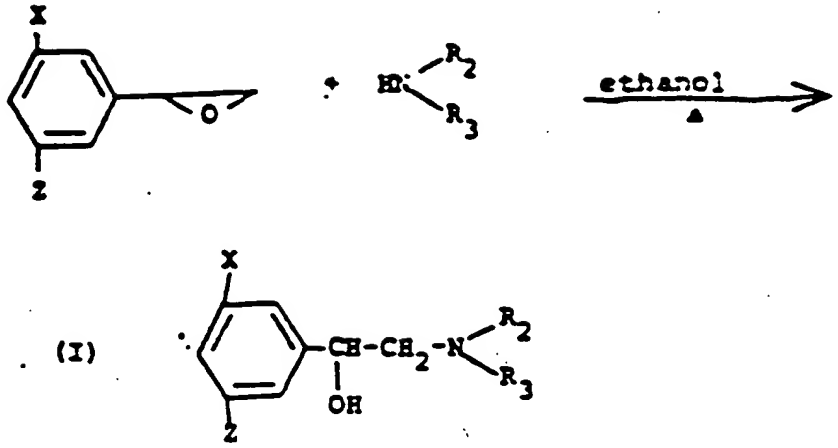


R_2 and R_3 are substituents other than hydrogen, except when R_3 is an alkyl or a substituted alkyl group which contains a tertiary carbon attached to nitrogen; and when R_8 is C_1-C_4 alkyl, or C_3-C_4 alkeryl, R_9 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkeryl; and further provided that when X and Z are halogen and Y is hydrogen or NH_2, then R_4 cannot be hydrogen, OH or OR_6 where R_6 is C_1-C_6 alkyl. Racemic mixtures of the above identified compounds and the optically active isomers, and non-toxic pharmacologically acceptable acid addition salts thereof.

A preferred group of the novel compounds of this invention have the above structure wherein X = hydrogen or halogen; Y is hydrogen, NR_8R_9, or NH-COR_5; Z is halogen, CN, CF_3, COOR, $CONH_2$, methyl, methoxy, NO_2, C_1-C_4 dialkylaminomethyl; R_1 is hydrogen, or methyl, R_2 is hydrogen, C_1-C_4 alkyl, C_3-C_4 alkeryl, C_2-C_4 alkanoyl or benzoyl; R_3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 alkeryl, benzyl; with the above provisos, and further provided that when X and Z are halogen and Y is hydrogen or NH_2, then R_4 cannot be hydrogen, OH or OR_6 when R_6 is C_1-C_6 alkyl.

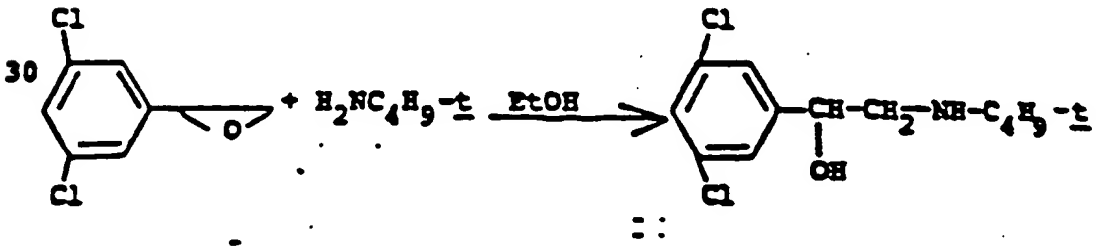
A most preferred group of novel compounds of this invention have the above structure wherein X = hydrogen, chlorine, bromine; Z is chlorine, bromine, CN, CF_3, COOH, $COOCH_3$, $COOC_2H_5$, $CONH_2$; R_1 is hydrogen; R_2 is hydrogen, C_1-C_4 alkyl; R_3 is hydrogen, C_1-C_4 alkyl; with the above provisos, and further provided that when X and Z are halogen and Y is hydrogen or NH_2, then R_4 cannot be hydrogen, OH or OR_6 where R_6 is C_1-C_6 alkyl.

It is found, that formula (I) compounds below (wherein Y is hydrogen) can be prepared by the condensation of an appropriately substituted styrene oxide with the appropriately substituted amine in the presence of an inert solvent, such as a lower alcohol at or near the boiling point of same, as shown below:



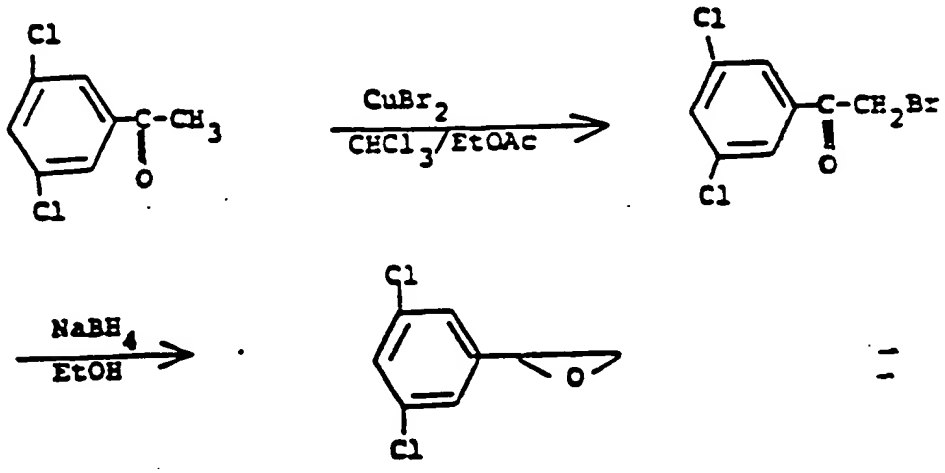
(I)

wherein X and Z are halogen, R_2 and R_3 are as hereinabove defined and Y is hydrogen. Thus, 3,5-dichlorostyrene oxide can be reacted with an equimolar or molar excess of t-butylamine in ethanol at reflux from about one to about eight hours, or until the reaction is essentially complete and the desired α-[(t-butylamino)methyl]-3,5-dichlorobenzyl alcohol is obtained as illustrated below:



The thus obtained product can be purified by known procedures, such as chromatography or recrystallization of salts thereof.

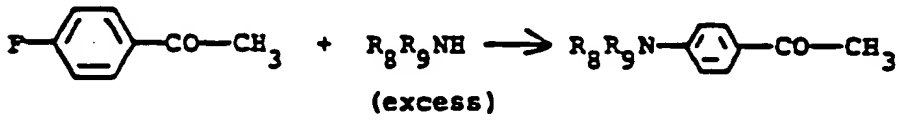
The above styrene oxide is made by reducing the corresponding phenacyl bromide with $NaBH_4$ at or below 5°C in the presence of an anhydrous lower alcohol, such as ethanol. The phenacyl bromide intermediate is prepared by brominating the appropriately substituted acetophenone with $CuBr_2$ in the presence of chloroform and ethyl acetate. The above sequence may be graphically illustrated as follows:



Alternatively, a formula (I) compound wherein Y is hydrogen may be prepared from the corresponding formula (I) compound wherein Y is amino, via a deamination reaction, by dissolving the amine in 50-52% aqueous

hypophosphorous acid (H_3PO_2). The solution is chilled below 10°C, and an equimolar or excess amount of sodium nitrite is added to an aqueous solution with stirring over a period of time. On completion of the addition, the reaction mixture is warmed to room temperature and stirred for an additional period of time. The product is then recovered from the reaction mixture by standard laboratory procedures and purified if so desired.

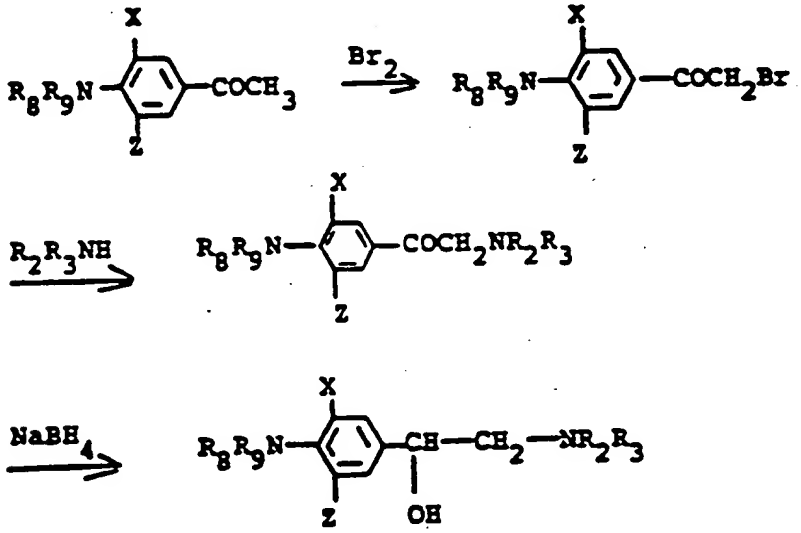
The preparation of 4-substituted aminoacetophenones required for the preparation of 4-substituted phenylethane derivatives which are now found to be useful for raising meat-producing animals, is exemplified as follows:



The fluorine displacement is carried out with excess amine in the presence or absence of a solvent; and if a solvent is required, water appears to be the most useful. With volatile amines, the reaction is conducted in a sealed vessel and generally temperatures of 50 - 100°C are sufficient to complete the reaction.

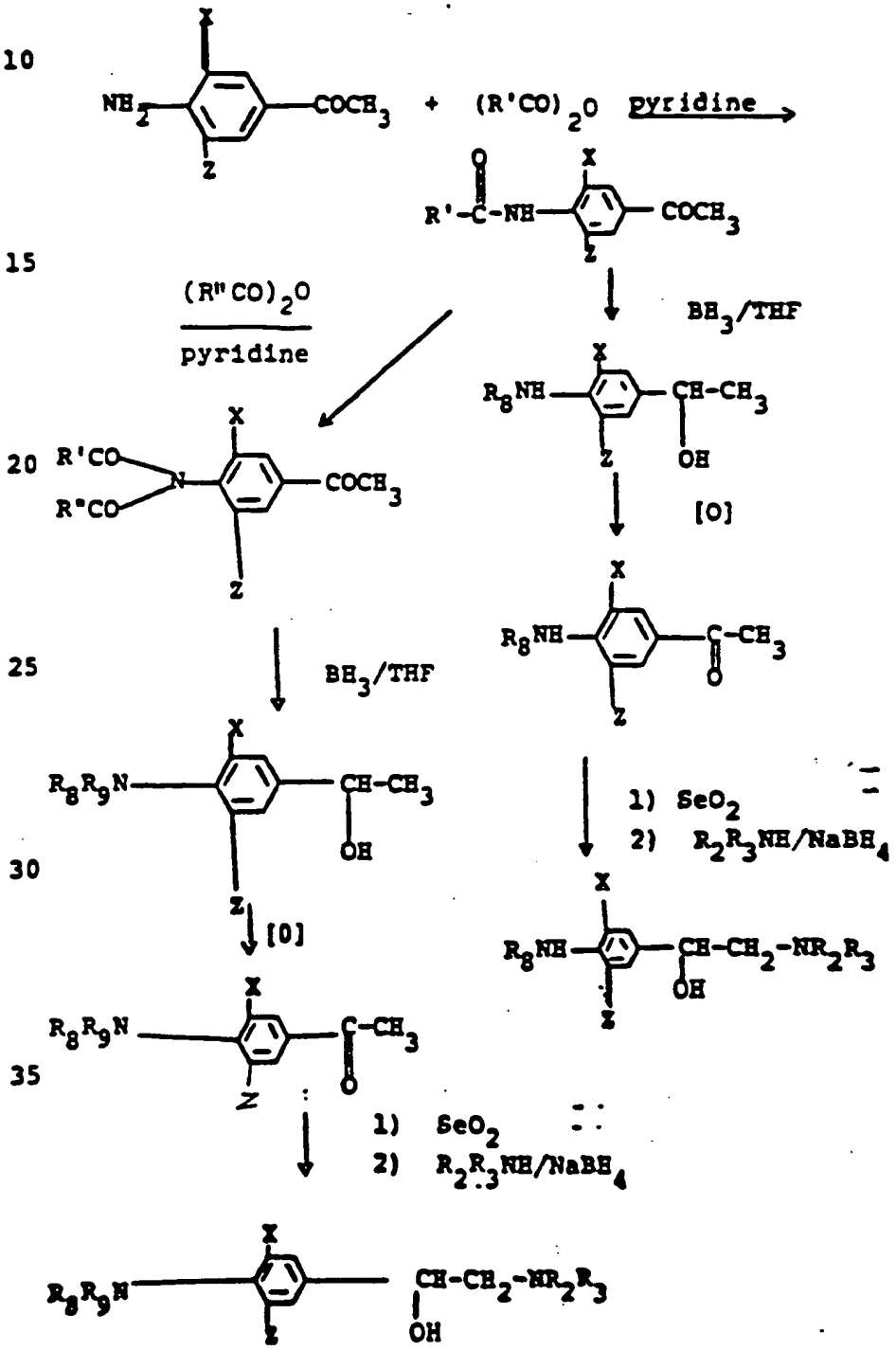
Chlorination and bromination of these aminoacetophenones may be conducted with N-chlorosuccinimide and N-bromosuccinimide in toluene, chlorobenzene or dichlorobenzene at 90 - 100°C. Iodination may be conducted with NaI/N,N-dichlorobenzenesulfonamide or iodine monochloride in acetic acid.

By reacting these acetophenones with bromine in chloroform or methylene chloride, the corresponding phenacyl bromides are prepared. These phenacyl bromides are then reacted with R_2R_3N amines and the aminoketones are reduced with $NaBH_4$ or $NaCNBH_3$ by conventional techniques described in references cited hereinbefore. Naturally, compounds which contain groups reactive to halogen, such as when R_8 is alkenyl, require other approaches that are discussed below.



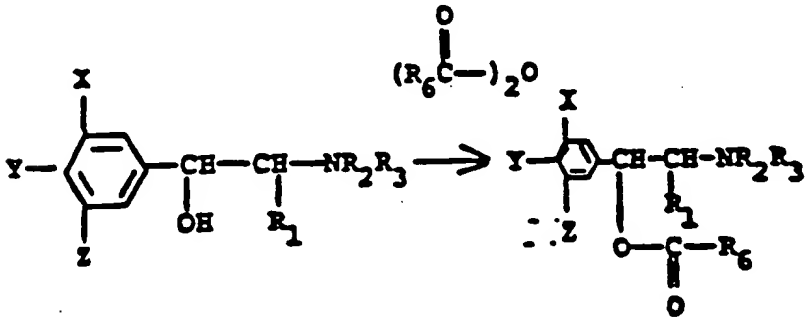
wherein X and Z are hydrogen, chlorine, or bromine and R_2 and R_3 are hydrogen, C_1-C_4 alkyl, or C_2-C_3 alkenyl groups.

The compounds of formula I, wherein R_8 and R_9 are groups other than both being hydrogen are also prepared by the following general scheme:



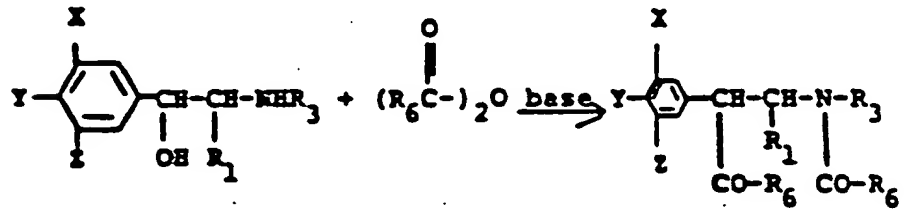
The methods utilized in the above scheme are either reported in references cited hereinbefore or by conventional methods. Oxidation of the alcohol may be conducted with chromic acid (Jones Reagent), MnO_2, pyridinium chlorochromate, or other oxidizing agents. Where X or Z are the BH_3-reducible groups, CN, COOR, or $CONH_2$, the appropriate acetophenones are prepared by displacement of X or Z represented by bromine with CuCN/DMF at 100 - 160°C by the conventional method, after reduction of the acylated aminoacetophenones in the first step followed by re-oxidation in the second step of the above procedure. The cyano substituted-amino-acetophenones are then converted to their corresponding ethanolamines, which are then converted to the desired esters, acids, and amides by conventional methods, such as R_1OH/acid $\rightarrow$ esters, hydrolyses $\rightarrow$ acids and partial hydrolyses $\rightarrow$ amides.

Furthermore, compounds of the following structure are prepared by allowing the corresponding ethanolamines to react with an equivalent or slight excess of the acid anhydrides with or without organic bases such as tertiary amines or pyridine. The reactions are conducted in inert solvents

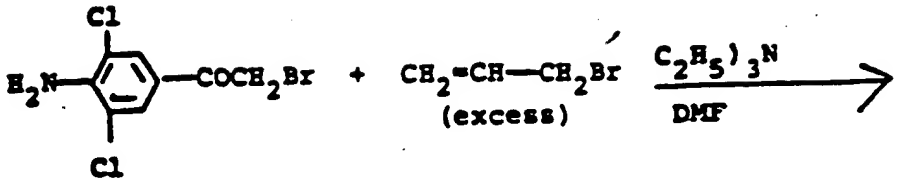


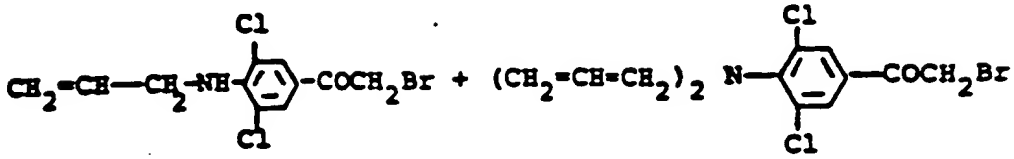
such as chlorinated hydrocarbons, or aromatic solvents at 0 - 25°C. Reaction of the anhydride at the hydroxyl group proceeds well provided R_2 and R_3 are groups other than hydrogen and when R_2 is hydrogen, R_3 is a substituent containing a tertiary carbon attached to nitrogen.

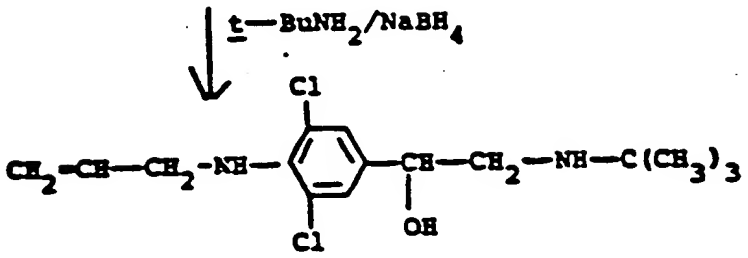
Compounds of the following structure which contain alkanoyl or aroyl groups on ethanolamine moiety are readily prepared by using two equivalents or more of the acid anhydrides in the presence of a tertiary amine, such as triethylamine, or pyridine in an inert solvent (CH_2Cl_2, $CHCl_3$, toluene, etc.) at 50 - 100°C.



Additionally, Formula I compounds, wherein R_8 and R_9 are selected from hydrogen and C_3-C_4 alkenyl, are prepared by alkenylation of 4-amino-3,5-disubstituted phenacyl bromides in dimethylformamide (DMF) in the presence of an acid acceptor, such as triethylamine or sodium carbonate, at 70 - 100°C to afford mono- and dialkenylated products which are separated and converted to I by conventional methods. The following scheme illustrates above-described general method:

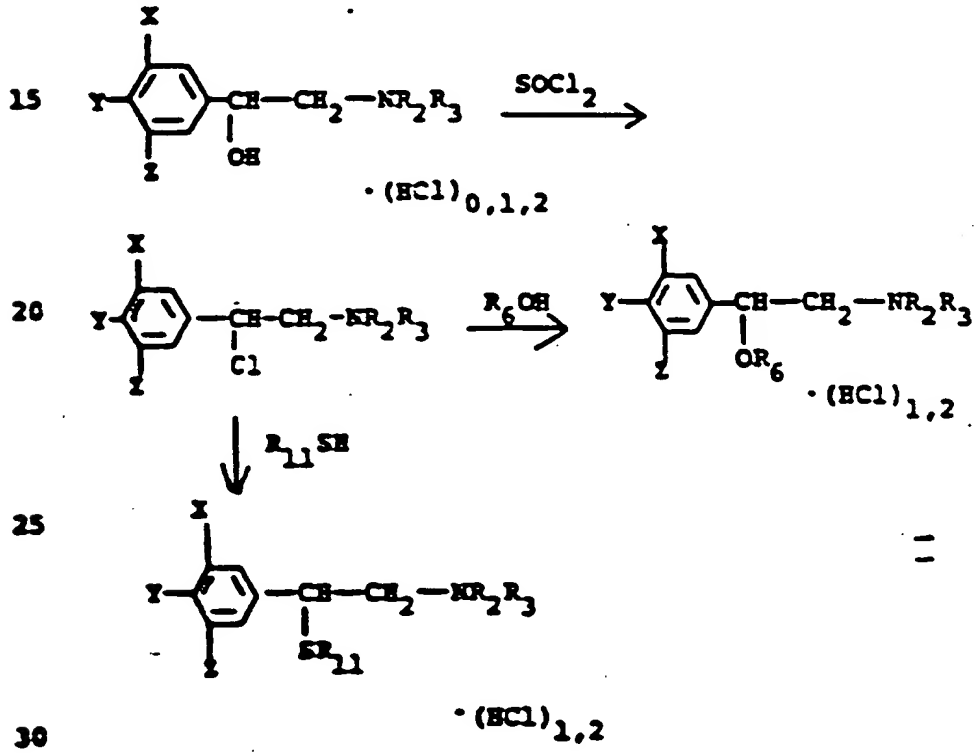






Formula (I) compounds wherein R_4 is OR_6 and SR_{11}, wherein R_6 and R_{11} are as hereinabove defined, may be prepared by converting the alcohol (R_4=OH) with thionyl chloride under an inert blanket of gas such as nitrogen at a temperature range of from about 0 to 10°C and preferably at 0 to 5°C for a reaction period sufficient to essentially complete the reaction. The thus obtained

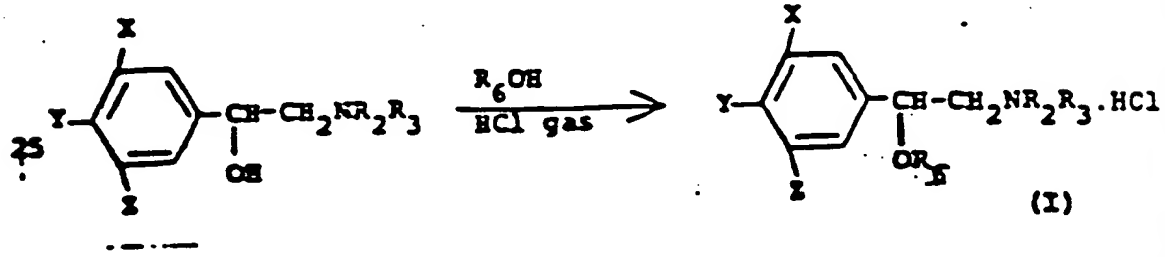
halo compound is isolated by conventional methods and is then reacted with the appropriate alcohol or mercaptan, under an inert blanket of gas, such as nitrogen at a temperature range of from about 0 to 50°C. The formula (I) product thus obtained is then isolated by standard laboratory methods and purified, if so desired. The above reaction sequence may be graphically illustrated as follows:



wherein X, Y, Z, R_2, R_3, R_6 and R_{11} are as hereinabove defined.

These displacement reactions may also be performed by using an excess of alkoxide (R_6O^-) or mercaptide ($R_{11}S^-$) in an inert solvent such as tetrahydrofuran to afford the above ethers and thioethers in a similar manner.

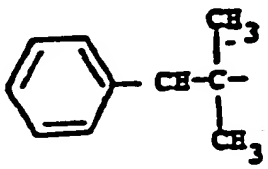
Alternatively, a formula (I) compound wherein R_4 is OR_6 may be prepared by dissolving the corresponding formula (I) compound wherein R_4 is OH in the corresponding R_6OH alcohol and saturating the thus obtained solution with dry HCl gas. The reaction mixture is then stirred at room temperature for a period of time sufficient to essentially complete the reaction and the product is then isolated by standard laboratory procedures and purified, if so desired. This reaction sequence may be illustrated as follows:



(I)

wherein X, Y, Z, R_2, R_3 and R_6 are as hereinabove defined.

In the present specification and claims, the term α,α-dimethylbenethyl means a structure having the following configuration:



When orally administered in the feed, generally about 0.01 to 300 grams per ton of feed of the above-identified phenylethane derivative or acid addition salt thereof, is effective for enhancing the growth rate and improving the efficiency of feed utilization by the above-mentioned meat-producing animals.

Since the effective and preferred dietary levels of the active ingredient vary somewhat from species to species in the above-mentioned animals, said levels for each animal species are listed in Table I below on a gram per ton of feed basis:

TABLE I

Compound	Effective Feed Level g/Ton	Preferred Level g/Ton	Animal
Formula (I)	0.1-200	1-100	Sheep, Goats
	0.01-50	0.1-10	Chickens, Rabbits
	0.01-50	0.1-10	Turkeys
	0.1-300	1-100	Cattle & Swine

Animal feed compositions which will provide the desired growth promotion and feed efficiency in the above-mentioned animals can be prepared by admixing the phenylethane derivative or acid addition salt thereof, or an animal feed supplement containing said compound, with a sufficient quantity of an appropriate animal feed to provide the desired level of active compound in said feed.

Animal feed supplements can be prepared by admixing about 10% to 75% by weight of the phenylethane derivative of acid addition salt thereof, with about 90% to 25% by weight of a suitable carrier or diluent. Carriers suitable for use to make up the feed supplement compositions include the following: alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal sodium chloride, cornmeal, can molasses, urea, bone meal, corncob meal and the like. The carrier promotes a uniform distribution of the active ingredient in the finished feed into which the supplement is blended. It thus performs an important function by ensuring proper distribution of the active ingredient throughout the feed.

If the supplement is used as a top dressing for feed, it likewise helps to ensure uniformity of distribution of the active material across the top of the dressed feed.

For parenteral administration, the phenylethane derivative may be prepared in the form of a paste or pellet and administered as an implant, usually under the skin of the head or ear of the animal in which enhanced growth rate and/or improved efficiency of feed utilization is sought.

In practice, parenteral administration generally involves injection of a sufficient amount of the above-said phenylethane derivative to provide the animal with from 0.001 to 50 mg/kg of body weight of the active ingredient. The preferred dosage level for cattle is the range of from 0.001 to 25 mg/kg of body weight of the active phenylethane derivative. The preferred dose level of said phenylethane derivative for poultry is about 0.001 to 35 mg/kg of animal body weight and the preferred dose level of said phenylethane derivative for sheep and goats is 0.001 to 40 mg/kg of animal body weight. The preferred dose level for rabbits is 0.001 to 35 mg/kg of animal body weight.

Paste formulations can be prepared by dispersing the active phenylethane derivative in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil or the like.

Pellets containing an effective level of the phenylethane derivative can be prepared by admixing the above-said active ingredient with a diluent such as carbowax, biodegradable polymers, carnauba wax, or the like. A lubricant, such as magnesium stearate or calcium stearate may be added to improve the pelleting process if desired.

It is, of course, recognized that more than one pellet may be administered to an animal to achieve the desired dose level which will provide the increased growth rate and/or improve efficiency of feed utilization by said animal. Moreover, it has been found that additional implants may also be introducted periodically during the treatment period in order to maintain the proper drug release rate in the animal's body.

In addition to enhanced growth promotion and improved efficiency of feed utilization by meat-producing animals, the compounds of the present invention have the added advantage that, at selected levels of administration, they increase the deposition of lean meat (i.e., muscle or protein) in said animals and improve the carcass quality thereof by increasing the ratio of lean meat to fat in the animals receiving them. This biological response has substantial advantage to poultrymen, cattlemen, and swine, sheep and goat producers since administration of said compounds at selected levels yields leaner animals which command premium prices from the meat industry.

These and other advantages of the present invention will become apparent from the examples set forth below. Such examples are provided only by way of exemplification and are not intended to be expressions of limitations on the invention.

EXAMPLE 1

Evaluation of Test Compounds as Animal Growth Promoters

CFI female mice from Carworth Farms are received when they are six weeks old. They are housed ten to a cage in air-conditioned rooms (72°F to 76°F) with automatically controlled lights, 14 hours on and 10 hours off. The basal diet used in these studies is Purina Laboratory Chow (see description below), which is supplied ad libitum. Water is allowed ad libitum.

Thirteen days after arrival, the mice are weighed in groups of ten and assigned at random to the different treatments. The concentration of the different compounds in the diet is indicated in the following tables. Twelve days later the mice are weighed again, and the experiment terminated. Test data are provided in Table II below wherein data are reported as percentage gain over controls. Different control animals are used for each test. The following is description of the diet to which the growth-promoting compounds were added.

DIET

Guaranteed Analysis

Crude protein not less than	23.0%
Crude fat not less than	4.5%
Crude fiber not more than	6.0%
Ash not more than	9.0%

Ingredients

Meat and bone meal, dried skimmed milk, wheat germ meal, fish meal, animal liver meal, dried beet pulp, ground extruded corn, ground oat groats, soybean meal, dehydrated alfalfa meal, cane molasses, animal fat preserved with BHA, vitamin B_{12} supplement, calcium pantothenate, choline chloride, folic acid, riboflavin supplement, brewer's dried yeast, thiamin, niacin, vitamin A supplement, D-activated plant sterol, vitamin E supplement, calcium carbonate, dicalcium phosphate, iodized salt, ferric ammonium citrate, iron oxide, manganous oxide, cobalt carbonate, copper oxide, zinc oxide.

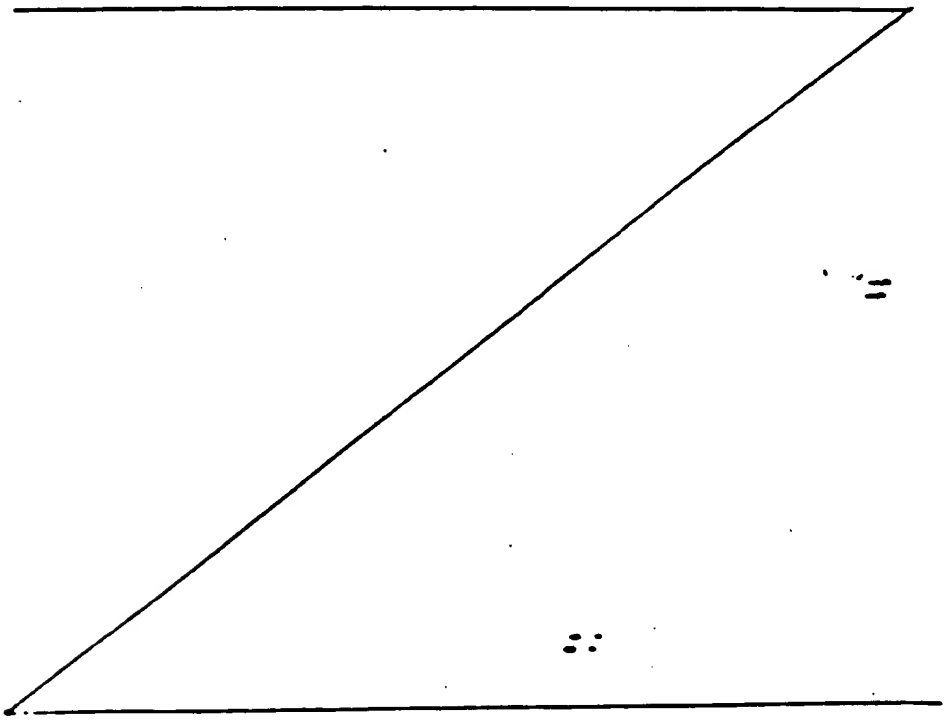


TABLE II

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
4'-[2-(tert-butylamino)-1-hydroxyethyl]-2'-chloroacetanilide	200 100	16.8 18.4	+107.9 +127.7
4-Amino-α-[(tert-butylamino)methyl]-3,5-diiodobenzyl alcohol hydrochloride	200 100	21.1 20.0	+27.1 +20.5
4-Amino-N-tert-butyl-3,5-dichlorophenethylamine hydrochloride	50	12.3	7.9
α-(Aminomethyl)-m-chlorobenzyl alcohol hydrochloride	200	15.8	+4.6
4-Amino-α-[(tert-butylamino)methyl]-3,5-diiodobenzyl alcohol hydrochloride	200 100	21.1 20.0	+27.1 +20.5

TABLE II (continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
α-[(Tert-butylamino)methyl]-3,5-dichloro-4-dimethylaminobenzyl alcohol	200	16.0	0
	50	21.9	+36.9
4-Amino-3,5-dichloro-α-[[(3-phenylpropyl)amino]methyl]benzyl alcohol	200	16.9	+ 5.6
	50	18.9	+18.1
α-[(Tert-butylamino)methyl]-3,5-dichloro-4-methylaminobenzyl alcohol	200	19.4	+21.3
	50	24.4	+52.5
4-Amino-N-tert-butyl-3,5-dichloro-β-isopropoxyphenethylamine	200	14.8	- 7.5
	50	20.9	+30.6
4-Amino-N-tert-butyl-3,5-dichloro-β-ethoxyphenethylamine hydrochloride	200	15.9	+30.3
	50	22.8	+86.9
Methyl-p-[3-[(4-amino-3,5-dichloro-β-hydroxyphenethyl)amino]propyl]benzoate	200	24.3	+22.6
	50	19.0	- 4.1

TABLE II (continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
Methyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocarbanilate	50	27.9	+40.8
4'-[2-(Tert-butylamino)-1-hydroxyethyl]-2',6'-dichloroacetanilide hydrochloride	200 50	21.8 23.4	+37.1 +47.2
5-[2-(Tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile	200 50	27.3 26.2	+90.9 +83.2
4-Amino-β-(benzyloxy)-N-tert-butyl-3,5-dichlorophenethylamine hydrochloride	200 50	22.6 22.4	+58.0 +56.6
α-[(Tert-butylamino)methyl]-3,5-dichloro-4-isopropylaminobenzyl alcohol	200 50 12 3	24.6 24.3 28.0 27.3	+72.0 +69.9 +95.8 +90.8

TABLE II (continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
5-[2-(Tert-butylamino)-1-hydroxyethyl]-anthranilonitrile	200 50	29.6 29.9	+79.4 +81.2
Methyl-5-[2-(tert-butylamino)-1-hydroxy-ethyl]-3-chloroanthranilate hydrochloride	200 50	24.4 20.1	+47.9 +21.8
4'-[2-Tert-butylamino)-1-hydroxyethyl] -2',6'-dichlorovaleranilide	200 50	26.1 26.4	+58.2 +60.0
Benzyl-4-[2-(tert-butylamino)-1-hydroxy-ethyl]-2,6-dichlorocarbanilate	50	25.1	+52.1
4-Amino-N-tert-butylamino-3,5-dichloro -β-(methylthio)phenethylamine hydrochloride	200 50	25.4 25.3	+55.8 +55.2
N-Tert-butyl-3,5-dichloro-β-methoxy-phenyethylamine hydrochloride	200 50	21.5 25.8	+50.3 +80.4

TABLE II (continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
3-Bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]-anthranilonitrile	200	16.1	+50.5
	50	24.2	+126.2
4-Amino-α-[(tert-butylamino)methyl]-3-methyl-benzyl alcohol	100	20.8	+94.5
4-(Butylamino)-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol	200	19.3	+80.4
	50	19.4	+81.3
2-Amino-3-bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]benzamide	200	17.4	+62.6
	50	19.8	+85.0
4-Amino-α-[(tert-butylamino)methyl]-3,5-dichloro-benzyl alcohol acetate (ester)	200	14.6	+36.4
	50	19.1	+78.5

TABLE II (continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
3-Bromo-5-[2-tert-butylamino)-1-hydroxyethyl]-anthranilic acid	200	18.2	+70.1
	50	13.6	+27.1
N-tert-butyl-3,5-dichloro-β-methoxy-4-methyl-aminophenethylamine hydrochloride	200	18.0	+68.2
	50	23.1	+115.9
α-[(tert-butylamino)methyl]-3,5-dichloro-4-(hexylamino)benzyl alcohol	200	19.6	+83.2
	50	20.7	+93.5
4-Amino-α-[(tert-butylamino)methyl]-3,5-dichloro-benzyl alcohol acetate (ester), acetate	200	14.4	+34.6
	50	18.7	+74.8
4-Benzylamino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol	200	15.7	+46.7
	50	16.4	+53.3

TABLE II (continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
β-(allyloxy)-4-amino-N-tert-butyl-3,5-dichloro-phenethylamine	200	21.5	+100.9
	50	19.6	+83.2
4'-[2-(tert-butylamino)-1-hydroxyethyl]-2',6'-dichlorobenzanilide	200	18.3	+71.0
	50	13.9	+29.9
4-(allylamino)-α-[(tert-butylamino)methyl]-3,5 dichlorobenzyl alcohol	200	20.2	+88.8
	50	21.9	+104.7
4'-[3-(tert-butylamino)-1-hydroxyethyl]-2',6'-dichloroacetanilide acetate (ester), hydrochloride	200	25.8	+141.1
	50	16.2	+51.4
N-(4-amino-3,5-dichloro-β-hydroxyphenethyl)-N-tert-butylacetamide acetate (ester)	200	18.7	+74.8
	50	15.0	+40.2

TABLE II (continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
α-[(tert-Butylamino)methyl]-3,5-dichloro-4-cyclohexylaminobenzyl alcohol	100	23.0	+115.0
α-[(tert-Butylamino)methyl]-4-amino-3-chloro-5-methylbenzyl alcohol, hydrochloride	200	16.5	+54.2
	50	19.7	+84.1

EXAMPLE 2

Antilipogenic Evaluation of Test Compounds - Mouse Study

CFI female mice, 55 days old, are weighed in groups of 10 and allotted to cages to minimize weight variation among cages. Treatments are randomly assigned to cages.

Each of the treatments are tested in 3 replicates, i.e., in 3 cages of 10 mice each. There are 10 cages of 10 control mice each. Drugs are mixed in the diet at the dosage level indicated. Feed and water are offered ad libitum for 12-day test period. Feed spilled is collected during the test period. At the end of the test period, the collected feed is weighed and the mean feed consumption per cage of ten mice is determined for each treatment. The mice are weighed as a group of 10 and the weight gain determined. The mice are sacrificed by cervical dislocation. The right uterine fat pad of each mouse is removed. The fat pads for each cage of 10 mice are weighed as a unit.

Data obtained are reported in Table III. Data are reported as percent reduction in fat pad weight. Reduction in fat pad weights of animals is generally indicative of reduction of total body fat of the treated animals.

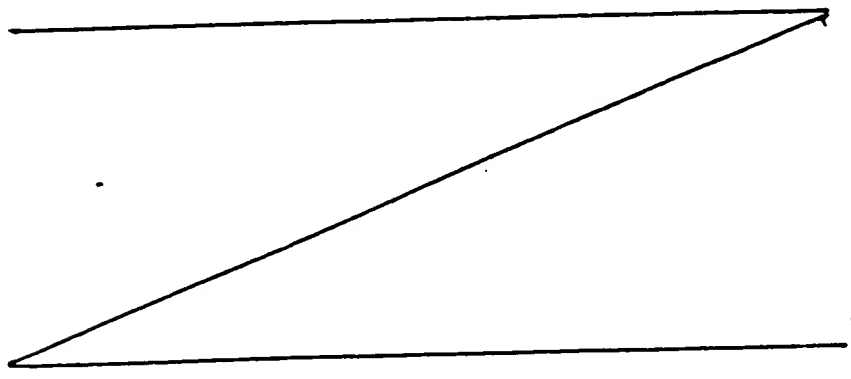


TABLE III

ANTILIPOGENIC EVALUATION OF TEST COMPOUNDS - MOUSE STUDY

COMPOUND	DOSAGE (PPM)	% REDUCTION IN FAT PAD WEIGHT VS CONTROLS
α-[(Tert-butylamino)methyl]-3,5-dichloro-4-dimethylamino benzyl alcohol	200	-46.1
	50	-14.8
4-Amino-3,5-dichloro-α-[[(3-phenyl-propyl)amino]methyl] benzyl alcohol	200	-41.1
	50	-36.2
4-Amino-3,5-dichloro-α[[(α,α-dimethylphenethyl)amino] methyl]benzyl alco ol hydrochloride	200	-13.1
	50	-13.9
α-[(Tert-butylamino)methyl]-3,5-dichloro-4-methylamino-benzyl alcohol	200	-51.0
	50	-41.9
4-Amino-N-tert-butyl-3,5-dichloro-β-isoproxyphenethylamine	200	-57.0
	50	-17.0
4-Amino-N-tert-butyl-3,5-dichloro-β-ethoxyphenethylamine hydrochloride	200	-33.7
	50	-15.3

TABLE III (Continued)

ANTILIPOGENIC EVALUATION OF TEST COMPOUNDS - MOUSE STUDY

COMPOUND	DOSAGE (PPM)	% REDUCTION IN FAT PAD WEIGHT VS CONTROLS
Methyl-4-(3-[(4-amino-3,5-dichloro-β-hydroxyphenethyl) amino]propyl)benzoate	200	-27.7
	50	-14.6
Methyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocarbonilate	50	-23.5
4'-[2-(Tert-butylamino)-1-hydroxyethyl]-2,6-dichloro-acetanilide hydrochloride	200	-27.1
	50	- 8.8
5-[2-Tert-butylamino-1-hydroxyethyl]-3-chloroanthranilonitrile	200	-45.9
	50	-10.4
4-Amino-β-(benzyloxy)-N-tert-butyl-3,5-dichloro-phenethylamine hydrochloride	200	-24.2
	50	-18.4
α-[(Tert-butylamino)methyl]-3,5-dichloro-4-isopropylaminobenzyl alcohol	200	-52.5
	50	-22.6
	12	- 6.3
	3	-25.5

TABLE III (Continued)

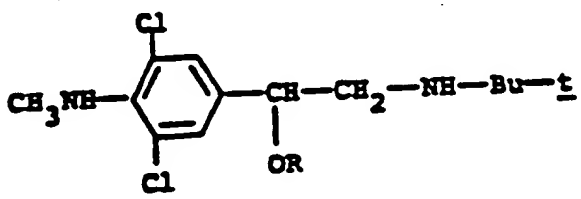
ANTILIPOGENIC EVALUATION OF TEST COMPOUNDS - MOUSE STUDY

COMPOUND	DOSAGE (PPM)	% REDUCTION IN FAT PAD WEIGHT VS CONTROLS
4^1-[2-(Tert-butylamino)-1-hydroxyethyl]-2^1,6^1-dichlorovaleranilide	200	-33.2
	50	-16.1
Benzyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocarbanilate	50	-19.6
Methyl-5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilate hydrochloride	200	- 5.9
	50	- 5.8
5-[2-(Tert-butylamino)-1-hydroxyethyl]anthranilonitrile	200	-41.5
	50	-10.3
4-[Amino-N-tert-butyl-3,5-dichloro-β-(methylthio) phenethylamine hydrochloride	200	-28.9
	50	-16.2
N-tert-butyl-3,5-dichloro-β-methoxyphenethylamine hydrochloride	200	-22.5
	50	-10.4

Example 3

N-tert-butyl-3,5-dichloro-β-methoxy-4-methylaminophenethylamine hydrochloride

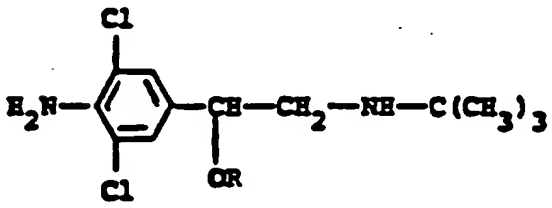
A 7 g sample of α-[(tert-butylamino)methyl]-3,5-dichloro-4-methylaminobenzyl alcohol is added to 70 ml of thionyl chloride under N_2 atmosphere and the mixture is stirred for two hours. Excess thionyl chloride is removed in vacuo, and the glassy residue is dissolved in 50 ml of methanol. The solution is stirred for 1.5 hours and evaporated to dryness. The residue is dissolved in 100 ml of H_2O and extracted with 2 x 50 ml of CH_2Cl_2. The aqueous layer is neutralized with solid $NaHCO_3$ and extracted with CH_2CL_2. The extract is dried ($MgSO_4$) and evaporated to dryness in vacuo to give 4.1 g of semi-solid, which after trituration with ethyl ether affords 1.07 g of the title compound, mp 220 - 221°C. Similarly, the following ethers are prepared:



Alcohol	R
ethanol	C_2H_5
1-propanol	1-C_3H_7
2-propanol	2-C_3H_7
1-butanol	1-C_4H_9
2-butanol	2-C_4H_9
1-hexanol	n-C_6H_{13}
benzyl alcohol	benzyl
allyl alcohol	allyl
4-methoxybenzyl alcohol	4-methoxybenzyl
4-chlorobenzyl alcohol	4-chlorobenzyl
4-nitrobenzyl alcohol	4-nitrobenzyl
4-methylbenzyl alcohol	4-methylbenzyl
3,4-dimethylbenzyl alcohol	3,4-dimethylbenzyl
3,4-dimethoxybenzyl alcohol	3,4-dimethoxybenzyl
3,4-dichlorobenzyl alcohol	3,4-dichlorobenzyl
2-chlorobenzyl alcohol	2-chlorobenzyl
2-methylbenzyl alcohol	2-methylbenzyl

Example 4

In the manner described in Example 3, the following ethers are prepared by substituting the corresponding alcohols for methanol.



R	mp°C
benzyl	190-193
allyl	57- 59
4-methoxybenzyl	
4-chlorobenzyl	
4-nitrobenzyl	
4-methylbenzyl	
3,4-dimethylbenzyl	
3,4-dimethoxybenzyl	
3,4-dichlorobenzyl	
phenyl	oil
4-chlorophenyl	
4-methoxyphenyl	
4-methylphenyl	
2-chlorophenyl	
4-nitrophenyl	

Example 5

N-tert-Butyl-3-chloro-5-cyano-β-methoxy-4-aminophenethylamine hydrochloride

In the manner described in Example 3, α-[(tert-butylamino)methyl]-4-amino-3-chloro-5-cyanobenzyl alcohol is converted into the title compound, and, similarly, the following are also prepared:

$$Ar\text{-}\underset{\underset{OCH_3}{|}}{CH}\text{-}CH_2\text{-}NH\text{-}R\cdot HCl$$

Ar	R
4-amino-3,5-dicyanophenyl	t-butyl
4-amino-3-chloro-5-trifluoromethylphenyl	t-butyl
4-amino-3-chloro-5-trifluoromethylphenyl	i-propyl
4-acetamido-3,5-dichlorophenyl	t-butyl
4-acetamidophenyl	t-butyl
4-amino-3-chloro-5-H_2N-CO-phenyl	t-butyl
4-amino-3-chloro-5-HO-CO-phenyl	t-butyl
4-amino-3-chloro-5-methylphenyl	t-butyl
4-amino-3-chloro-5-methoxyphenyl	t-butyl
4-amino-3-chloro-5-nitrophenyl	t-butyl
4-amino-3-chloro-5-CH_3O-CO-phenyl	t-butyl
4-amino-3-chloro-5-dimethylaminomethylphenyl	t-butyl
4-amino-3-cyano-phenyl	t-butyl

Example 6

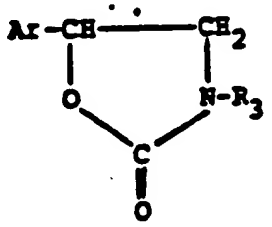
5-(4-amino-3,5-dichlorophenyl)-3-tert-butyl-2-oxazolidinone

In 10 ml of CH_2CL_2, 0.5 g of 4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol is stirred with 1 ml of Et_3N at -5°C and 2 ml of 12.5% $COCl_2$ in benzene/5 ml of CH_2CL_2 is added over 15 minutes. The resulting suspension is stirred 20 minutes at 1°C and allowed to warm to room temperature with stirring for 1.5 hours. The mixture is evaporated to dryness, and the residue is chromatographed on silica gel with 1:1 hexane/CH_2CL_2 to afford 0.1 g of

oil which crystallizes to give the title compound, mp 97 - 103°C.

In the same manner, α-[(allylamino)methyl] -4-amino-3,5-dichlorobenzyl alcohol is allowed to react with phosgene to afford 5-(4-amino-3,5-dichlorophenyl)-3-allyl-2-oxazolidinone.

Likewise, the following compounds are prepared by this manner:



Ar	R_3
3,5-dichlorophenyl	t-butyl
3,5-dichlorophenyl	i-propyl
4-acetamidophenyl	t-butyl
4-amino-3-chloro-5-cyanophenyl	t-butyl
4-amino-3-chloro-5-trifluoromethylphenyl	t-butyl
3-chloro-4-acetamidophenyl	t-butyl
3,5-dichloro-4-methylaminophenyl	t-butyl
3,5-dichloro-4-ethylaminophenyl	t-butyl
3,5-dichloro-4-i-propylaminophenyl	t-butyl
3,5-dichloro-4-acetamidophenyl	t-butyl
3,5-dichloro-4-methoxycarbonylaminophenyl	t-butyl
3,5-dichloro-4-benzyloxycarbonylaminophenyl	t-butyl

Ar	R_3
3,5-dichloro-4-methyl-carbamoylaminophenyl	t-butyl
4-amino-3-chloro-5-methylphenyl	t-butyl
4-amino-3-cyanophenyl	t-butyl
4-amino-3-trifluoromethyl-phenyl	t-butyl
4-amino-3-chloro-5-NH_2CO-phenyl	t-butyl
4-amino-3-chloro-5-HOOC-phenyl	t-butyl
4-amino-3-chloro-5-CH_3OOC-phenyl	t-butyl
4-amino-3-chloro-5-$(CH_3)_2NCH_2$-phenyl	t-butyl
4-amino-3,5-dicyanophenyl	t-butyl

Example 7

4-Amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol acetate

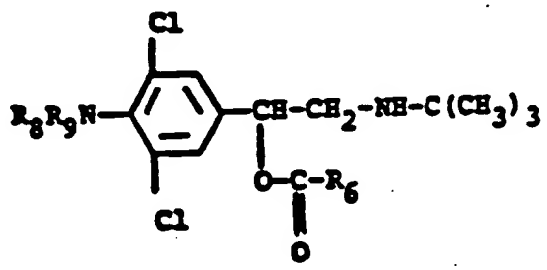
A mixture containing 1 g of 4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol in 35 ml of CH_2Cl_2 at 10 - 15°C is stirred, and 0.37 g of Ac_2O and 0.5 ml of Et_3N are added dropwise. The reaction mixture is then allowed to warm to room temperature, and the reaction is followed by thin-layer chromatography to completion. The mixture is evaporated to dryness in vacuo, and the yellow viscous liquid (1.5 g) is stirred with 50 ml of ethyl

ether to afford a yellow solid (0.84 g), mp 128 - 131°C. This material is shown by nuclear magnetic resonance spectroscopy and by neutralization with alkali to be the acetic acid salt. On treating 100 mg of this salt in 30 ml of CH_2Cl_2 with 30 ml of 10% aqueous NaOH, the salt is neutralized. The CH_2Cl_2 solution is dried ($MgSO_4$) and evaporated to dryness in vacuo to afford the viscous title compound. Analysis: Calcd for $C_{14}H_{20}O_2N_2Cl_2$: C, 52.67; H, 6.32; N, 8.78; Found: C, 52.38; H, 6.51; N, 8.88.

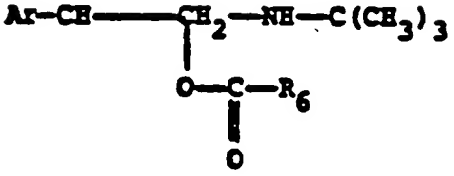
In the same manner, propionic anhydride, butyric anhydride, pivalic anhydride, and benzoic anhydride are allowed to react with 4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol (A) and α-[(tert-butylamino)methyl]-3,5-dichloro-4-methylamino-benzyl alcohol (B) respectively, to afford the propionate, butyrate, pivalate and benzoates of A and B.

Example 8

The following esters are prepared by the method of Example 7 by using the appropriate acid anhydride.



R_8	R_9	R_6
H	CH_3	CH_3
H	C_2H_5	CH_3
H	$n\text{-}C_3H_7$	CH_3
H	$2\text{-}C_3H_7$	CH_3
H	benzyl	CH_3
H	allyl	CH_3
CH_3	CH_3	CH_3
H	CH_3	C_2H_5
H	$CH_3O\text{-}CO\text{-}$	CH_3
H	$CH_3NH\text{-}CO$	CH_3
H	CH_3	$n\text{-}C_4H_9$
C_2H_5	C_2H_5	CH_3
$n\text{-}C_4H_9$	$n\text{-}C_4H_9$	CH_3



Ar	R_6
3,5-dichlorophenyl	$2\text{-}C_3H_7$
4-amino-3-chloro-5-cyanophenyl	CH_3
4-amino-3-chloro-5-trifluoromethylphenyl	CH_3
4-amino-3-chloro-5-H_2NCO-phenyl	CH_3
4-amino-3-chloro-5-HOOC-phenyl	CH_3
4-amino-3-chloro-5-methylphenyl	CH_3
4-amino-3-bromo-5-cyanophenyl	CH_3
4-amino-3-chloro-5-CH_3OCO-phenyl	CH_3
4-amino-3-chloro-5-$(CH_3)_2NCH_2$-phenyl	CH_3
4-amino-3,5-dicyanophenyl	CH_3
4-amino-3-cyanophenyl	$t\text{-}C_4H_9$

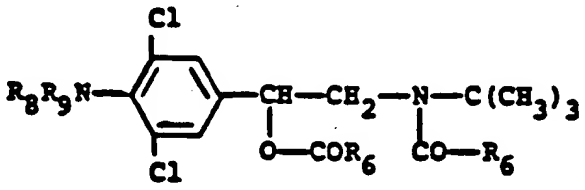
Example 9

N-(4-amino-3,5-dichloro-β-hydroxyphenethyl)-N-tert-butylacetamide acetate

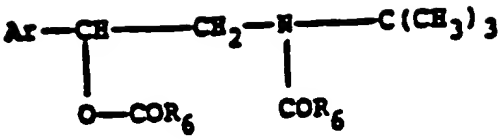
A mixture containing 2.5 g of 4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol, 25 ml of pyridine and 10 ml of acetic anhydride is stirred for three hours and evaporated to dryness in vacuo with heating up to 70°C. The residue is treated with ice, 100 ml of CH_2Cl_2 and 50 ml of 10% NaOH solution.

The CH_2Cl_2 phase is separated, and the aqueous portion is further extracted with CH_2CL_2 (2 x 50 ml). The combined CH_2CL_2 solutions are dried (Na_2SO_4) and evaporated to dryness to afford a solid after scratching. The solid is washed with hexane and collected to afford 2.61 g of the title compound, mp 126 - 136°C.

Similarly, by substituting the appropriate acid anhydrides, the following compounds are prepared.



R_8	R_9	R_6
H	CH_3	CH_3
H	C_2H_5	CH_3
H	2-C_3H_7	CH_3
H	n-C_4H_9	CH_3
CH_3	CH_3	CH_3
H	CH_3O-CO	CH_3
H	CH_3NH-CO	CH_3
H	CH_3CO	CH_3
H	CH_3	C_2H_5
C_2H_5	C_2H_5	n-C_4H_9



Ar	R_6
4-amino-3,5-dicyanophenyl	C_2H_5
4-amino-3-chloro-t-dimethyl-amino methylphenyl	CH_3
4-amino-3-chloro-5-CH_3OOC-phenyl	C_2H_5
4-amino-3-chloro-5-methylphenyl	CH_3
3,5-dichlorophenyl	CH_3
4-amino-3-chloro-5-cyanophenyl	CH_3
4-amino-3-chloro-5-trifluoro-methylphenyl	CH_3
4-amino-3-chloro-5-H_2NCO-phenyl	CH_3

Example 10

4-Acetamido-α-[(tert-butylamino)methyl]-3,5-dichloro-benzyl alcohol acetate

In 15 ml of CH_2CL_2, 1.57 g of 4-acetamido-β-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol is suspended and stirred while 1.2 g of triethylamine in 30 ml of 30 ml of CH_2Cl_2 is added, followed by 0.7 g of acetic anhydride in 15 ml of CH_2CL_2. The mixture is stirred for 20 hours and then is washed with 100 ml of 10% NaOH solution. The organic phase is separated, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue is dissolved in 30 ml of ethanol and a trace of H_2O is added, followed by 10% HCl to acidify. The mixture is evaporated to dryness *in vacuo* and the residue is crystallized from acetone/hexane (30 ml/3 ml). This affords 1.35 g, mp. 254 - 257°C dec., of the title compound.

Similarly, by replacing acetic anhydride with propionic anhydride, butyric anhydride, pivalic anhydride, and benzoic anhydride, the corresponding propionate, butyrate, pivalate, and benzoate esters are prepared.

Example 11

α-[(tert-Butylamino)methyl]-m-hydroxybenzyl alcohol acetate

In the manner described in Example 10 m-(benzyloxy)-α-[(tert-butylamino)methyl]benzyl alcohol is converted to m-(benzyloxy)-α-[(tert-butylamino)-methyl]benzyl alcohol acetate. This material is then debenzylated to give α-[(tert-butylamino)methyl]-m-hydroxybenzyl alcohol acetate.

Example 12

5-(p-Aminophenyl)-3-tert-butyl-2-oxazolidinone

In 270 ml of CH_2Cl_2, 12.97 g of α-[(tert-butylamino)methyl]-p-nitrobenzyl alcohol is dissolved. The solution is cooled to -5°C and 54 ml of 12.5% phosgene in benzene is added slowly. After the addition is completed, the mixture is stirred for 3.5 hours and poured on ice. The organic phase is separated, and the aqueous layer is extracted with CH_2Cl_2 (2 X 100 ml). The combined organic layers are washed with saturated $NaHCO_3$ solution (2 X 250 ml), 100 ml of H_2O and dried over $MgSO_4$. The solution is evaporated to dryness to give 16.3 g, which is recrystallized from MeOH twice to afford 12.58 g of 3-tert-butyl-5-(p-nitrophenyl)-2-oxazolidinone, mp 123 - 125°C. This product (10 g) is dissolved in 200 ml of MeOH and hydrogenated

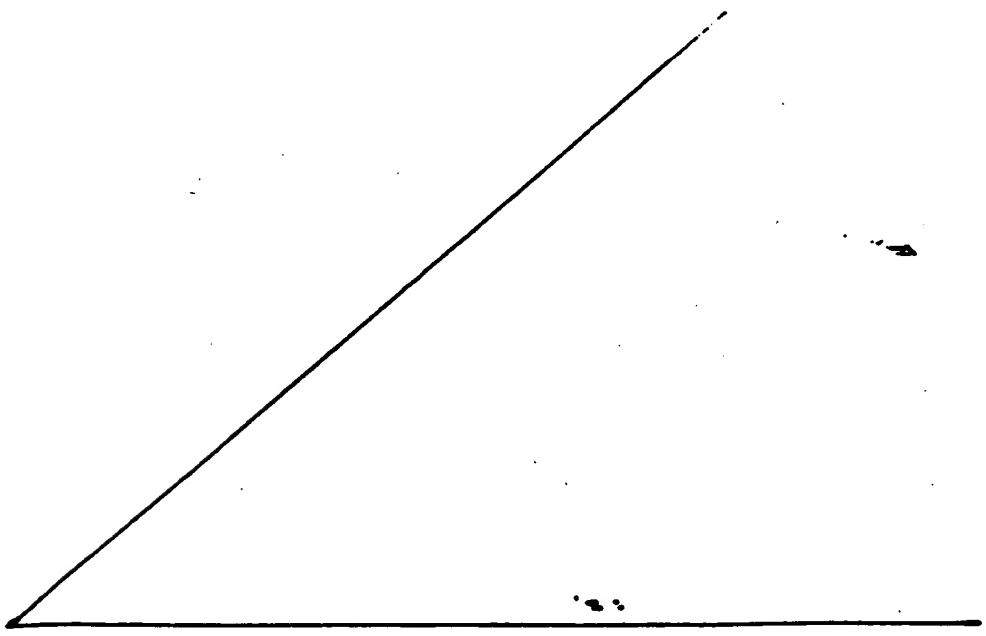
over 6 g of Raney nicke at 51 p.s.i.g at 40°C to give, after filtration and evaporation, 8.21 g of 5-(p-aminophenyl)-3-tert-butyl-2-oxazolidinone, mp 125 - 129°C.

Example 13

α-[(tert-butylamino)-methyl]3,5-dichloro-4-dimethylaminobenzyl alcohol

A mixture containing 50 g of p-fluoroacetophenone and 150 ml of 40% aqueous dimethylamine is warmed in a pressure bottle at 90 - 100°C. After two hours, a pale yellow oil is formed. The mixture is cooled, and the oil solidifies. The solid is collected and washed well with H_2O to give 54.93 of p-dimethylaminoacetophenone, mp 101 - 103°C, after heptane recrystallization. A 72 g sample of this acetophenone is heated with 129 g of N-chlorosuccinimide in 700 ml of toluene to reflux temperature and maintained at this temperature for 35 minutes. The mixture is cooled and filtered. The filter cake is washed with 200 ml of toluene, and the filtrate and wash solution are evaporated to dryness in vacuo to afford 66 g of oil. This oil is chromatographed on SiO_2 with 40% hexane/CH_2Cl_2 to give 38.9 g of 3.5-dichloro-4-dimethylaminoacetophenone as a yellow oil. A 5.22 g sample of this oil is added portionwise to 2.75 g of SeO_2 in 20 ml of dioxane and 0.7 ml of H_2O at 55 - 60°C. This mixture is heated at reflux temperature for 4.5 hours, cooled and filtered through siliceous earth. The filter cake is washed with 20 ml of dioxane. The dioxane solutions are cooled to 15°C and 2.77 g of t-butylamine is added dropwise to afford a tan precipitate. After stirring 15 minutes at room temperature,

the mixture is diluted with 200 ml of ethanol, cooled to 5°C and 7 g of $NaBH_4$ is added portionwise. After 15 hours, the mixture is treated with 300 - 400 g of ice and 200 ml of H_2O at below 10°C. The mixture is stirred to dissolve all solids and extracted with 300 ml of CH_2Cl_2. The CH_2Cl_2 layer is washed with 100 ml of H_2O, dried ($MgSO_4$) and evaporated to dryness in vacuo to give 5.6 g of orange oil. This oil is dissolved in ethyl ether, decolorized with activated carbon and concentrated to 15 ml. On cooling, crystals are obtained. The title product is collected as white crystals, mp 96 - 99°C.

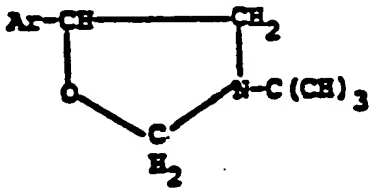


EXAMPLE 14

5-(4-amino-3,5-dibromophenyl)-3-tert-butyloxazolidine

A mixture containing 2 g of 4-amino-3,5-dibromo-α-[(tert-butylamino)methyl]benzyl alcohol and 5 ml of 37% formalin solution in 20 ml of toluene containing a few crystals of p-toluene sulfonic acid is heated at reflux to azeotrope water. After three hours, the mixture is cooled, diluted to 75 ml with CH_2Cl_2 and washed with 10% aqueous NaOH solution (2x20 ml). The aqueous portion is further extracted with 10 ml of CH_2Cl_2 and the combined organic extracts are dried ($MgSO_4$) and evaporated to dryness in vacuo to afford 1.6 g of clear brown oil. A chemical ionization mass spectrographic analysis gives a Mass + H^+ of 377, which is correct for the title compound. The nuclear magnetic resonance proton spectrum reveals a singlet at δ4.53 in $CDCl_3$ indicative of the O-CH_2-N group in the title compound.

In the same manner, the following oxazolidines are prepared by substituting the corresponding arylethanolamines for 4-amino-3,5-dibromo-α-[tert-butylamino)methyl]benzyl alcohol.



Ar
4-amino-3,5-dichlorophenyl
4-methylamino-3,5-dichlorophenyl
4-amino-3-chloro-5-cyanophenyl
4-amino-3-chloro-5-trifluromethylphenyl
4-amino-3-chloro-5-methylphenyl
4-amino-3-bromo-5-NH_2-CO-phenyl
4-amino-3-bromo-5-HOOC-phenyl
4-acetamido-3,5-dichlorophenyl
3,5-dichloro-4-methoxycarbonylaminophenyl
3,5-dichloro-4-methylcarbamoylaminophenyl
4-amino-3-cyanophenyl
4-amiro-3-trifluromethylphenyl
4-amino-3,5-dicyanophenyl

EXAMPLE 15

4-Benzylamino-α-[tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol

In the manner described in Example 13 the title compound is prepared to give mp 86-89°C.

EXAMPLE 16

4'-[2-(tert-butylamino)-1-hydroxyethyl]-2',6'-dichlorobenzanilide

A mixture containing 2.04 g of 4-amino-3,5-dichloroacetophenone and 0.25 ml of triethylamine in 10 ml of benzoyl chloride is stirred and heated at 130-135° for two hours. The mixture is cooled, filtered and the product is washed with ether. This amide is further oxidized with SeO_2 in the manner described in Example 13 to eventually afford the title compound, mp 177-182°C.

EXAMPLE 17

α-[(tert-butylamino)methyl]-3,5-dichloro-4-methylamino-benzyl alcohol

p-Methylaminoacetophenone is prepared and chlorinated by method described in Example 29 to give 3,5-dichloro-4-methylaminoacetophenone. This ketone (18 g) in 200 ml of $CHCl_3$ is stirred and 4.65 ml of Br_2 in 50 ml of $CHCl_3$ is added dropwise. After the addition is completed, the mixture is stirred an additional 20 minutes and warmed to reflux temperature for 25 minutes. The mixture is cooled, 100 ml of H_2O is added and saturated Na_2CO_3 solution is added carefully until the mixture is neutral. The $CHCl_3$ layer is separated and the aqueous layer is further extracted with 100 ml of CH_2Cl_2. The combined extracts are dried ($MgSO_4$) and evaporated to dryness to afford 16.3 g of the phenacyl bromide. This material (16 g) in 80 ml of EtOH is stirred at 12-15°C and 40 ml of t-butylamine is added dropwise. After the addition is completed the mixture is stirred for 10 minutes at 12-15°C and then cooled to 5° and 4 g of $NaBH_4$ is carefully added. After stirring for 0.5 hours, the mixture is allowed to warm to room temperature and stirring is continued for 0.75 hours. The mixture is poured on 300 ml of ice with stirring and the resulting mixture is extracted with 300 ml of CH_2Cl_2. The CH_2Cl_2 extract is dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give a yellow oil. Trituration of this residue with ethyl ether affords 7.45 g of the title compound, which melts at 98-101°C after recrystallization from ethyl ether.

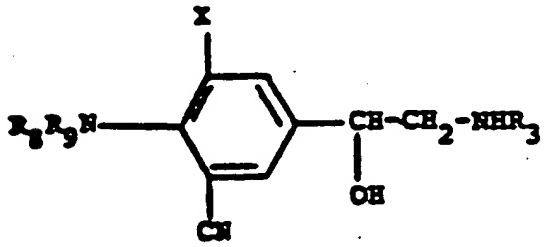
EXAMPLE 18

5-[2-(tert-butylamino)-1-hydroxyethyl]anthranilonitrile

A mixture containing 48.86 g of p-amino-acetophenone in 490 ml of toluene is stirred while 64.5 g of N-bromosuccinimide is added in portions over 0.5 hours at below 40° C. After 15 minutes, the mixture is washed with H_2O (4x100 ml). The solution is dried ($MgSO_4$) and evaporated to dryness to afford 70.53 g of 4-amino-3-bromoacetophenone, mp 59-62°C. A 35 g sample of this material in 180 ml of dry dimethylformamide is stirred and heated at reflux with 17.57 g of $Cu_2(CN)_2$ for 6 hours under N_2 atmosphere. Subsequently, 180 ml of $FeCl_3$/HCl solution (40 g $FeCl_3.6H_2O$/10 ml concentrated HCl/60 ml H_2) is added and the mixture is heated for 20 minutes at 60-70°C and poured into 350 ml of H_2O. The aqueous mixture is extracted with CH_2Cl_2 and the extracts are washed with H_2O, saturated $NaHCO_3$ solution and H_2O, respectively. The CH_2Cl_2 solution is evaporated to dryness in vacuo and the residue is recrystallized from 95% EtOH to afford 14.25 g, mp 155-159°C, of 4-amino-3-cyanoacetophenone. A 4.8 g sample of this product in 100 ml of EtOAc and 100 ml of $CHCl_3$ containing 13.32 g of $CuBr_2$ is heated at reflux temperature for 20 minutes. The mixture is further heated after 20 ml of EtOH is added and then filtered while still hot. The filter cake is washed with 50 ml of hot 20% MeOH/CH_2Cl_2 and the combined organic solutions are evaporated to dryness in vacuo. The residue is stirred in 25 ml of CH_2Cl_2 and the solid is collected and washed with CH_2Cl_2 to give 8.08 g of the phenacyl bromide. This material is added to 50 ml of t-$BuNH_2$ in 100 ml of

EtOH at 5° under N_2 atmosphere. After 10 minutes of stirring, the mixture is allowed to warm to 30°C to give a solution. This solution is cooled to 10° and 4 g of $NaBH_4$ is added in portions. After 45 minutes, the mixture is allowed to warm (42°C) and kept at 20°C until the exotherm subsides. The mixture is then evaporated to dryness and the residue is washed with H_2O. The residue is dried and treated with 200 ml of boiling MeOH and the hot MeOH solution is filtered. The filter cake is further washed with hot MeOH and the combined filtrates are concentrated to afford crystals. This solid is recrystallized from MeOH/2-PrOH to afford 2.08 g, mp 184-186°C, of the title compound.

In a similar manner, the following related compounds are prepared starting with the appropriate acetophenone:



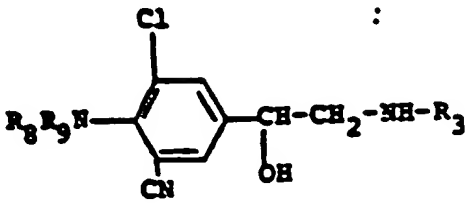
R_8	R_9	R_3	X
H	H	2-C_3H_7	H
H	CH_3	t-butyl	H
CH_3	CH_3	t-butyl	H
H	C_2H_5	t-butyl	H
H	n-C_3H_7	t-butyl	H
H	2-C_3H_7	t-butyl	H
H	n-C_4H_9	t-butyl	H
H	CH_3	2-C_3H_7	H
H	benzyl	t-butyl	H
C_2H_5	C_2H_5	t-butyl	Cl
n-C_3H_7	n-C_3H_7	t-butyl	Cl
n-C_4H_9	n-C_4H_9	t-butyl	Cl

EXAMPLE 19

3-chloro-5-[2-(tert-butylamino)-1-hydroxyethyl]-anthranilonitrile

In 100 ml of toluene, 5 g of 4-amino-3-cyanoacetophenone is heated at reflux temperature for 20 minutes with 4.2 g of N-chlorosuccinimide. The mixture is cooled and filtered. The filtrate is further heated at reflux temperature for 2 hours. The precipitate is collected and washed with H_2O. The remaining solid is treated with 0.75 ml of Br_2/14 ml of $CHCl_3$ added to 75 ml of $CHCl_3$ and 4.9 ml of EtOH. The mixture is evaporated to dryness and the residue is slurried with CH_2Cl_2, collected and washed with CH_2Cl_2 to afford 2.84 g of the phenacyl bromide. This material is allowed to react with t-$BuNH_2$ and reduced with $NaBH_4$ by the procedure of Example 18 to afford the title compound, mp 128-138°C.

In a similar manner, the following compounds are prepared:



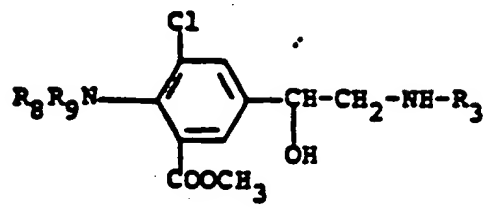
R_8	R_9	R_3
H	H	2-propyl
H	CH_3	t-butyl
CH_3	CH_3	t-butyl
H	C_2H_5	t-butyl
H	2-propyl	t-butyl
H	n-butyl	t-butyl
H	benzyl	t-butyl

EXAMPLE 20

5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloro-anthranilic acid, methyl ester, hydrochloride

A mixture containing 1.36 g of 5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile in 21 ml of 50% aqueous NaOH and 21 ml of EtOH is stirred under N_2 for 0.5 hours. The mixture is evaporated to remove EtOH and acidified to pH 3 and further evaporated to dryness in vacuo. The residue treated several times with MeOH and evaporated to dryness. The solid is then treated with a solution which is prepared from 40 ml of MeOH and 2 ml of acetyl chloride. After allowing to stand overnight, the mixture is filtered and the filtrate is evaporated to dryness. The filter cake is also washed with MeOH and added to preceding filtrate. The residue is dissolved in acetone, filtered, and evaporated to dryness. The solid is triturated with Et_2O and filtered to give 1.49 g, mp 95-115°C, of the title compound.

In a similar manner, the following related esters are prepared:



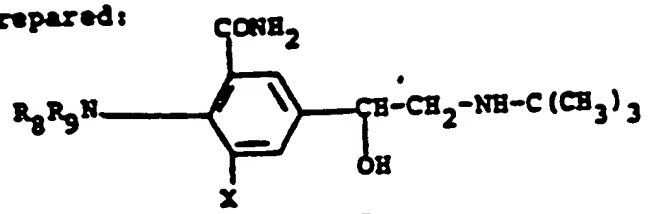
R_8	R_9	R_3
H	H	2-propyl
H	CH_3	t-butyl
CH_3	CH_3	t-butyl
H	C_2H_5	t-butyl
H	n-propyl	t-butyl
H	n-butyl	t-butyl
H	benzyl	t-butyl
H	allyl	t-butyl
C_2H_5	C_2H_5	t-butyl
n-C_4H_9	n-C_4H_9	t-butyl
n-C_3H_7	n-C_3H_7	t-butyl

EXAMPLE 21

2-Amino-3-bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]-benzamide

A mixture containing 1.02 g of 3-bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]anthranilonitrile in 25 ml of H_2O, 5 ml of 50% NaOH and 30 ml of EtOH is stirred and heated at 55-65°C under N_2 atmosphere for 1.25 hours. The mixture is evaporated to remove EtOH and extracted with $CHCl_3$. The $CHCl_3$ extract is washed with 25 ml of 2% NaOH, dried ($MgSO_4$) and evaporated to dryness to afford 0.74 g. This solid is stirred with pentane and filtered to afford 0.6 g, mp 135-145°C, of the title compound.

Similarly, the following compounds are prepared:



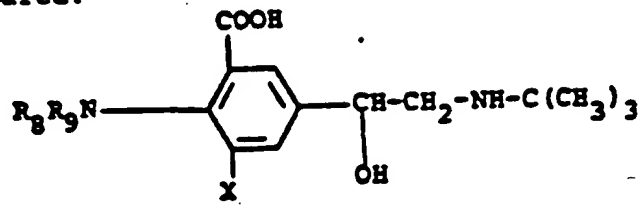
R_8	R_9	X
H	CH_3	Cl
H	H	Cl
H	C_2H_5	Cl
CH_3	CH_3	Cl
H	2-C_3H_7	Cl
H	n-C_4H_9	Cl
H	CH_3	Br
H	benzyl	Cl
C_2H_5	C_2H_5	Cl
n-C_3H_7	n-C_3H_7	Cl
n-C_4H_9	n-C_4H_9	Cl

EXAMPLE 22

3-bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]-anthranilic acid

A mixture containing 2 g of 3-bromo-5-[2-(tert-butylamino)-1-hydroxyethyl]anthranilonitrile in 10 ml of 50% NaOH, 50 ml of H_2O and 60 ml of EtOH is stirred and heated to reflux temperature under N_2 for an hour. The EtOH is evaporated and the aqueous mixture mixed with 50 ml of H_2O and 50 ml of $CHCl_3$. The $CHCl_3$ layer is removed and the interfacial brown oil is collected, added to 10 ml of MeOH, 5 ml of H_2O and this mixture is acidified to pH 5. After stirring for an hour, the off-white solid is collected, washed with H_2O and dried to give 0.8 g, mp 221.5°C dec., of the title compound.

Similarly, the following compounds are prepared:



R_8	R_9	X
H	H	Cl
H	CH_3	Cl
CH_3	CH_3	Cl
H	CH_3	Br
H	2-C_3H_7	Cl
H	n-C_4H_9	Cl
H	benzyl	Cl
C_2H_5	C_2H_7	Cl
n-C_3H_7	n-C_3H_7	Cl
n-C_4H_9	n-C_4H_9	Cl

EXAMPLE 23

5-(3-hydroxyphenyl)-3-tert-butyl-2-oxazolidinone

In the manner described in Example 8, m-benzyloxy)-α-[tert-butylamino)methyl]benzyl alcohol is coverted to the oxazolidinone compound by treatment with phosgene. Subsequently debenzylation is completed to give the title compound.

EXAMPLE 24

5-(3-hydroxyphenyl)-3-tert-butyloxazolidine

In the manner described in Example 12, m-(benzyloxy)-α-[(tert-butylamino)methyl]benzyl alcohol is reacted with formaldehyde to afford the oxazolidine derivative, which is debenzylated by the procedure of Example 10 to give the title compound.

EXAMPLE 25

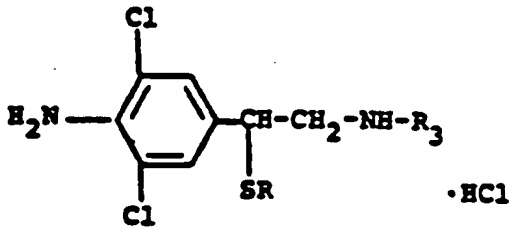
4-amino-N-tert-butyl-3,5-dichloro-β-(methylthio)-phenethylamine hydrochloride

In the manner described in Example 3, N-tert-butyl-3,5-dichloro-β-chloro-4-aminophenethylamine hydrochloride is prepared. An 11 g sample of this product is portionwise added to 5 ml of methyl mercaptan in 100 ml of dry ethylenedichloride at -10°C to 0°C. The mixture is stirred and allowed to rise gradually to room temperature over a four day period. The mixture is filtered, the filter cake is washed with ethylenedichloride (2x500 ml). The solid is dispersed in 200 ml of H_2O, cooled to 5°C and basified with 6N NaOH solution to give a white oil, which is extracted with CH_2Cl_2 (3x100 ml). The CH_2Cl_2 extract is dried ($MgSO_4$) and evaporated to dryness to give 6.41 g of dark green oil. This oil is stirred in HCl/isopropanol and the mixture is evaporated to dryness. The residue is stirred in 35 ml of ethyl ether for 16 hours and filtered to give 3.63 g, mp 178-181°C dec. This solid is heated in refluxing ethyl acetate and filtered to give 2.07 g, mp 188-193°C. Recrystallization from 75 ml of ethylenedichloride affords 1.45 g of the title compound, mp 191-196°C.

The title compound is also obtained by adding 5-10 fold excess of sodium mercaptide in tetrahydrofuran at 0-10°C and by following the above workup.

EXAMPLE 26

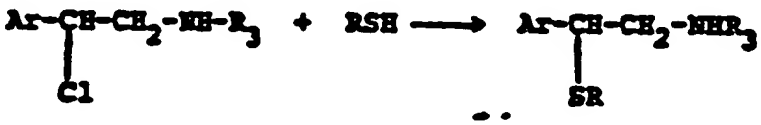
In the same manner as described in Example 25, the following thioethers are prepared by substituting methyl mercaptan with the corresponding mercaptans:



R	R_3
methyl	2-propyl
ethyl	t-butyl
2-propyl	t-butyl
n-butyl	t-butyl
t-butyl	t-butyl
n-hexyl	t-butyl
phenyl	t-butyl
benzyl	2-propyl

EXAMPLE 27

In the manner described in Example 25, substitution of the corresponding chloro compound for N-tert-butyl-3,5-dichloro-β-chloro-4-aminophenethylamine hydrochloride and adding the appropriate mercaptans afford the following thioethers:



Ar	R	R_3
4-amino-3-cyanophenyl	methyl	2-propyl
4-methylamino-3,5-dichlorophenyl	methyl	t-butyl
4-amino-3-chloro-5-trifluoromethyl	methyl	t-butyl
4-amino-3-chloro-5-cyanophenyl	methyl	t-butyl
4-amino-3-chloro-5-cyanophenyl	ethyl	t-butyl
4-acetamido-3,5-dichlorophenyl	methyl	t-butyl
4-amino-3-chloro-5-H_2NCO-phenyl	methyl	t-butyl
4-amino-3-chloro-5-HOCO-phenyl	methyl	t-butyl
4-amino-3-chloro-5-methylphenyl	ethyl	t-butyl
4-amino-3-chloro-5-methoxyphenyl	n-butyl	t-butyl
4-amino-3-chloro-5-nitrophenyl	methyl	t-butyl
4-amino-3-chloro-5-CH_3O-CO-phenyl	methyl	t-butyl

EXAMPLE 28

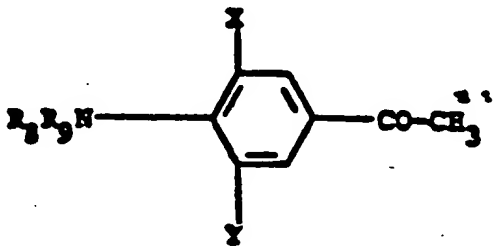
3,5-dichloro-4-(N,N-diethylamino)acetophenone

A sample (2.5 g) of 4-amino-3,5-dichloroacetophenone in 10 ml of acetic anhydride and 25 ml of pyridine is stirred and heated at reflux temperature for 20 hours. The mixture is evaporated to dryness, and the residue is treated with ice and 10% NaOH solution and extracted with CH_2Cl_2 (3x50-ml). The extracts are dried (Na_2SO_4) and evaporated to dryness to give 2.42 g of semisolid, which is purified by chromatography over SiO_2 using CH_2Cl_2 as eluent to afford 1.06 g of 4-(N,N-diacetyamino)-3,5-dichloroacetophenone as an oil. This material is dissolved in 10 ml of tetrahydrofuran (THF) under N_2 atmosphere and 18 ml of 1M BH_3·THF is added dropwise. The mixture is stirred until the reaction is complete and H_2O is added cautiously. The mixture

is evaporated to remove THF and 20 ml of H_2O and 10 ml of 10% NaOH are added. This aqueous mixture is extracted with CH_2Cl_2 (3x25 ml) and the extracts are dried (Na_2SO_4) and evaporated to dryness to yield 0.68 g the desired alcohol. This product (0.3 g) in 2 ml of CH_2Cl_2 is added to 0.32 g of pyridinium chlorochromate (PCC) in 2 ml of CH_2Cl_2. After 1.25 hours, an additional 0.3 g of PCC is added and after another 0.5 hours, the solution is decanted and the residue is washed with 10 ml of CH_2Cl_2. The combined CH_2Cl_2 solutions are diluted with 50 ml of CH_2Cl_2 and washed with 10 ml of saturated Na_2CO_3 solution and 10 ml of H_2O and dried (Na_2SO_4). The solution is evaporated to dryness to afford a residue which is chromatographed on SiO_2 with CH_2Cl_2 as eluent to yield 0.04 g of the title compound as an oil (NMR in $CDCl_3$: δ1.0 (6H, triplet), 2.5 (3H, singlet), 3.25 (4H, quartet), 7.83 (2H, singlet). The monoethylaminoacetophenone is also obtained as a solid (0.12 g) as the second component.

This 3,5-dichloro-ethylaminoacetophenone is further reacted with propionic anhydride, reduced and reoxidized in the above manner to afford 3,5-dichloro-N-ethyl-N-propylaminoacetophenone.

In a similar manner the following 4-(N,N-dialkylamino-acetophenones which are required for preparing 4-(N,N-disubstituted amino) compounds of formula I are prepared:



R_8	R_9	X	Y
n-C_3H_7	n-C_3H_7	Cl	Cl
n-C_4H_9	n-C_4H_9	Cl	Cl
C_2H_5	n-C_3H_7	Cl	Cl
C_2H_5	C_2H_5	Cl	CH_3
C_2H_5	C_2H_5	Cl	CF_3
C_2H_5	C_2H_5	Cl	NO_2
C_2H_5	C_2H_5	Cl	Br
C_2H_5	C_2H_5	Cl	OCH_3

EXAMPLE 29

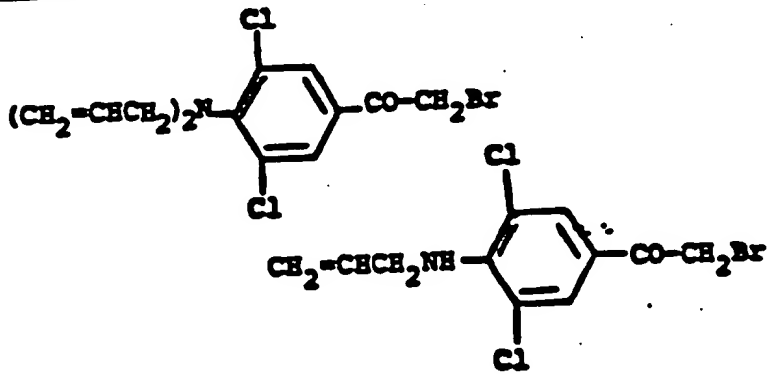
α-[(tert-butylamino)methyl]-3,5-dichloro-4-diethylaminobenzyl alcohol

In the manner described in Example 13, 3,5-dichloro-4-diethylaminoacetophenone is oxidized with SeO_2 and reductively alkylated with t-$BuNH_2/NaBH_4$ to afford the title compound, mp 93-96°C.

Similarly, α-[tert-butylamino)methyl]-3,5-dichloro-4-(n-dipropyl)aminobenzyl alcohol and α-[(tert-butylamino)methyl]-3,5-dichloro-4-(n-dibutyl)-aminobenzyl alcohol are prepared

EXAMPLE 30

2-bromo-3',5'-dichloro-4'-diallylaminoacetophenone and 4'-(allylamino)-2-bromo-3',5'-dichloroacetophenone



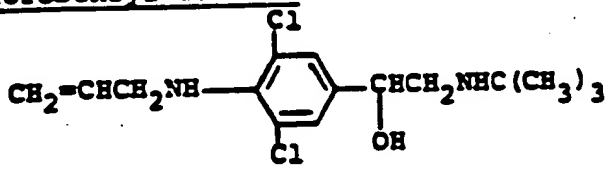
Triethylamine (17.0 g, 0.168 mol) is added in one portion to allyl bromide (105.9 g, 0.875 mol) under a nitrogen atmosphere. The resulting white emulsion gives an exotherm to 70°C and becomes a thick white solid mass within 5 minutes. The solution formed with the addition of ~100 ml of DMF is stirred for 1 hour at 70-95°C. A solution of 4'-amino-2-bromo-3',5'-dichloroacetophenone (25.0 g, 0.088 mol) in 50 ml of DMF is added in one portion and the resulting brown reaction mixture is maintained at 80-90°C for 2 hours. The progress of the reaction is frequently checked by thim layer chromatography (SiO_2/CH_2Cl_2/hexanes (1/1)) since prolonged heating results in the decomposition of both starting material and products. The reaction mixture is poured into 1.5l of H_2O and is stirred for 0.5 hours. After a second aqueous trituration, the residual brown semi-solids are stirred with ~150 ml of CCl_4 for 0.5 hours to form a suspension. The yellowish-brown solids are collected by filtration and are air dried to give 14.9 g (59.6%) of recovered phenacyl bromide starting material. The CCl_4 filtrate is stirred with $MgSO_4$, filtered and concentrated to yield 9.42 g of a brown syrup. Gradient elution (hexanes/CH_2Cl_2 (10/0 ⟶ 8/2) flash chromatography on a 9"x2" column of Silica Gel 60 gives two major fractions:

(A) 1.82 g (5.7%) of a faster moving amber syrup, identified as 2-bromo-3',5'-dichloro-4'-diallylaminoacetophenone by IR(neat) 1680 cm^{-1}; NMR ($CDCl_3$) δ7.93 (s, 2, AR-H), δ5.25-5.55 (complex m, 2, CH=), 5.40-4.95 (complex m, 4, CH_2=), 4.40 (s, 2, CH_2Br) and 3.87 (m resembling d, 4, J=6Hz, CH_2N); chemical ionization mass spectrum $(M + H)^+$ = 3.62; and

(B) 3.49 g (12.2%) of a slower moving brown syrup, identified as 4'-(allyamino)-2-bromo-3',5'-dichloroacetophenone by IR(neat) 3330, 1670cm^{-1}; NMR($CDCl_3$) δ7.83 (s, 2, AR-H), 6.35-5.65 (complex m, 1, CH=), 5.50-5.00 (complex m, 2, CH_2=), 4.84 (br t, 1, NH), 4.37 (s, 2, CH_2Br) and 4.20 (br m, 2, CH_2N); chemical ionization mass spectrum $(M + H)^+$ = 322.

EXAMPLE 31

4-(Allyamino)-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol



A solution of 4'-(allylamino)-2-bromo-3',5'-dichloroacetophenone (2.88 g, 8.92 mmol) in 10 ml is added dropwise over 1 hour to a stirred solution of t-butylamine (1.34 g, 18.3 mmol) in 20 ml of THF. The reaction temperature is maintained at -24°-13°C by cooling in a dry ice-CCl_4 bath. The resulting amber suspension is warmed to room temperature over 30 minutes and is stirred at 21-22°C for 1.5 hours. Sodium cyanoborohydride (2.80 g, 44.6 mmol) is added in two portions over 5 minutes to give a thick tan suspension with an exotherm from 22-25°C. Glacial acetic acid (~10 ml) is added dropwise to gradually form a yellow solution which is stirred at room temperature for 3 days. The reaction mixture is poured into a solution of 100 ml of H_2O and 100 ml of saturated aqueous NaCl which is then adjusted to pH7 with 10% Na_2CO_3 and extracted three times with Et_2O. The combined

extracts are shaken with two portions of diluted aqueous HCl which are combined, neutralized with 10% Na_2CO_3 to pH8 and extracted three times with Et_2O. After stirring the combined extracts with anh. K_2CO_3, the pale yellow-green solution is filtered and concentrated to yield 2.04 g (72.1%) of a pale yellow syrup, identified as 4-(allylamino)-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol by IR(neat) 3400 cm^{-1}; NMR($CDCl_3$) δ7.32 (s, 2, Ar-H), 6.35-5.60 (complex m, 1, CH=), 5.45-4.95 (complex m, 2, CH_2=), 4.52 (d of d, 1, Ar-CH), 3.97 (overlapping m, 3, Ar-$NHCH_2$), 3.03 (br s, 2, NH and OH), 2.68 (m, 2, CH_2N) and 1.13 (s, 9, $C(CH_3)_3$); chemical ionization mass spectrum $(M + M)^+$ = 317. The CH_2Cl_2/CH_3OH/conc. NH_4OH (80/19/1)) shows one major spot (R_f = 0.6) with nine trace impurities. The syrup gradually crystallizes to a tan solid on standing.

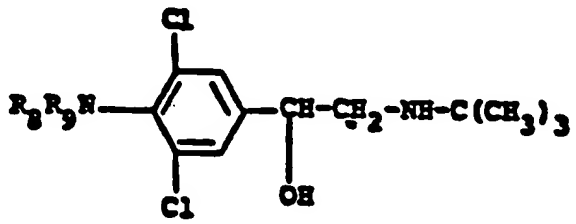
EXAMPLE 32

N-tert-butyl-m-hydroxy-β-methylthiophenethylamine hydrochloride

By using the procedure of Example 3 and substituting methyl mercaptan for methanol as in Example 25 the title compound is prepared.

EXAMPLE 33

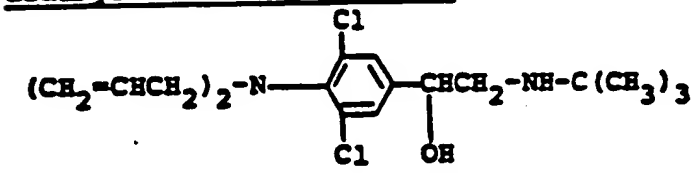
The following compounds are prepared by the method of Example 13:



R_8	R_9	mp °C.	
H	1-C_4H_9	oil	
H	1-C_6H_{13}	62-64	
H	C_2H_5	209	(HCl salt)
H	benzyl	85-89	
H	cyclopentyl	oil	
H	cyclohexyl	194-198	(HCl salt)
$-CH_2-CH_2-CH_2-CH_2-$			

EXAMPLE 34

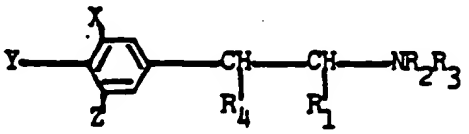
α-[(tert-butylamino)methyl]-3,5-dichloro-4-diallylaminobenzyl alcohol



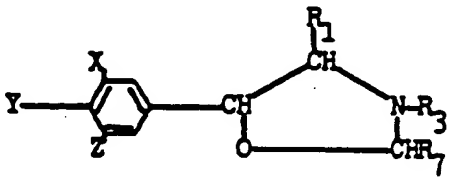
The title compound is prepared using the procedure described for the preparation of 4-(allylamino)-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol (Example 31). The pale yellow syrup, which gradually crystallizes on standing, is identified by IR(neat) 3300 and 1630 cm^{-1}; NMR($CDCl_3$) δ7.26 (s, 2, AR-H), 6.23-5.54 (complex m, 2, CH=), 5.32-4.87 (complex m, 4, CH_2=), 4.48 (m, 1, Ar-CH), 3.78 (m resembling d, 4, J-6Hz, Ar-NCH_2), 3.4-2.0 (br s, 2, NH and OH), 2.62 (m, 2, CH_2N) and 1.13 (s, 9, $C(CH_3)_3$); chemical ionization mass spectrum $(M + H)^+$ = 357, corresponding to that expected of the title compound.

CLAIM

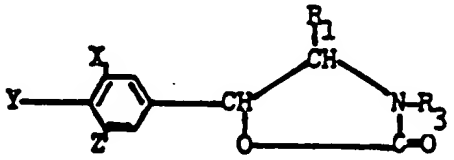
1. An animal feed composition comprising a balanced diet and from 0.01 to 400 grams per ton of feed of a compound having a formula selected from the group consisting of:



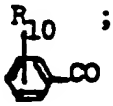
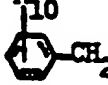
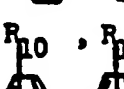
(I);

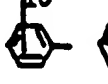
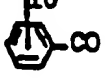
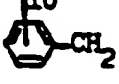


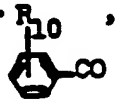
(Ia); and



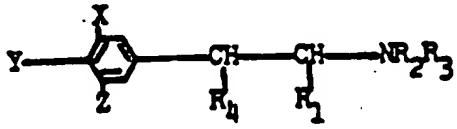
(Ib)

wherein, X is hydrogen, halogen or -CN; Y is hydrogen, NR_8R_9 or $NHCOR_5$; Z is hydrogen, halogen, OH, CN, CF_3, $COOR_1$, $CONH_2$, C_1-C_4 alkyl or C_1-C_4 alkoxy; R_1 is hydrogen, C_1-C_4 alkyl; R_2 is hydrogen, C_1-C_6 alkyl, C_3-C_4 alkenyl, C_2-C_5 alkanoyl or  ; R_3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, methoxypropyl, C_3-C_4 alkenyl, peryl, 2-hydroxyethyl, α,α-dimethylphenethyl, benzyl, 3-phenylpropyl or 3-(4-carbomethoxyphenyl)propyl; and when R_2 and R_3 are taken together with the nitrogen to which they are attached, they represent morpholino or N^1-C_1-C_4 alkylpiperazino; R_4 is hydrogen, OH, OR_6 or SR_{11}; R_5 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy,  ,  ;  or $N(R_1)_2$

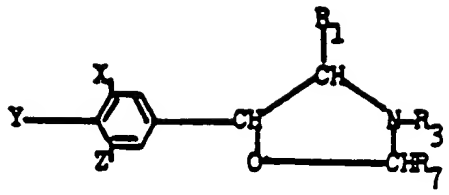
R_6 is C_1-C_6 alkyl, C_2-C_5 alkanoyl,  ,  ,  , C_3-C_4 alkenyl;

R_7 is hydrogen, C_1-C_4 alkyl or phenyl; R_8 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkenyl; R_9 is hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_3-C_4 alkenyl, or benzyl; and when R_8 and R_9 are taken together with the nitrogen to which they are attached, they represent pyrrolidino; R_{10} is chloro, dichloro, methyl, dimethyl, methoxy, dimethoxy or nitro; R_{11} is C_1-C_6 alkyl, phenyl or benzyl; with the provisos that when R_3 is phenyl, 2-hydroxyethyl, α,α-dimethylphenethyl, C_3-C_6 cycloalkyl, benzyl, methoxypropyl, 3-phenylpropyl, or 3-(4-carbomethoxyphenyl)propyl, R_2 is hydrogen; and when R_3 is hydroxyethyl, R_4 is hydroxyl and the compound is (I); and when R_6 is alkanoyl or  , R_2 and R_3 are substituents other than hydrogen, except when R_3 is an alkyl or a substituted alkyl group which contains a tertiary carbon attached to nitrogen; and when Y is hydrogen, X and Z are halogen, and R_2 is hydrogen, C_2-C_5 alkanoyl or  , R_3 is isopropyl, 2-butyl, and t-butyl; and when R_8 is C_1-C_4 alkyl or C_3-C_4 alkenyl, R_9 is C_1-C_4 alkyl or C_3-C_4 alkenyl; and when Z is OH, X and Y are hydrogen; and that at least one of X, Y and Z represents a substituent other than hydrogen; and when X is -CN, Z is -CN; and when Z is hydroxyethyl, R_4 is OH; and when Z is a group other than halogen, Y is NR_8R_9 or $NHCOR_5$; and when R_5 is $N(R_1)_2$, R_4 is OH; and further provided that when X is hydrogen or halogen, and Y is hydrogen, NH_2 or $NHCOR_5$, and Z is hydrogen, halogen or OH, then R_4 cannot be hydrogen, OH or OR_6 where R_6 is C_1-C_6 alkyl; racemic mixtures of the above - identified compounds and the optically active isomers, and non-toxic, pharmacologically acceptable acid addition salts thereof.

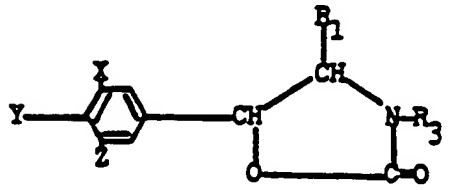
2. A method for the preparation of an animal feed composition comprising admixing an animal feed with from 0.01 to 400 grams per ton of feed of a compound having a structure selected from the group consisting of:



(I);



(Ia); and

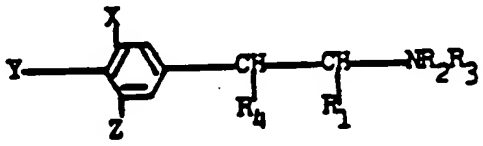


(Ib)

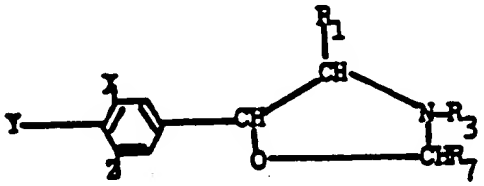
wherein X, Y, Z, R_1, R_2, R_3, R_4 and R_7, are as defined in claim 1 above.

3. A composition according to claim 1 wherein said compound is selected from the group consisting of: N-tert-butyl-3,5-dichloro-4-methoxy-4-methylaminophenethylamine; α-[(tert-butylamino)methyl]-3,5-dichloro-4-isopropylaminobenzyl alcohol; 5-[2-(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile; 5-[2-(tert-butylamino)-1-hydroxyethyl]anthranilonitrile; methyl-5-[2-(tert-butylamino)-1-hydroxyethyl)-3-chloroanthranilate; 4'-[2-tert-butylamino)-1-hydroxyethyl]-2',6'-dichlorovaleranilide; benzyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocarbanilate; 5-acetylanthranilonitrile; 4-amino-N-tert-butyl-3,5-dichloro-4-(methylthio)phenethylamine; N-tert-butyl-3,5-dichloro-4-methoxyphenethylamine; α-[(tert-butylamino)-methyl]-3,5-dichloro-4-methylaminobenzyl alcohol; α-[(tert-butylamino)methyl-3,5-dichloro-4-dimethylaminobenzyl alcohol; 4-amino-3,5-dichloro-α-[[(3-phenylpropyl)amino]methyl]benzyl alcohol; 4-amino-3,5-dichloro-α-[[α,α-dimethylphenethyl)amino]methyl]benzyl alcohol; 4-amino-N-tert-butyl-3,5-dichloro-4-ethoxyphenethylamine; methyl-p-(3-[(4-amino-3,5-dichloro-4-hydroxyphenethyl)amino]propyl)benzoate; methyl-4-[2-(tert-butylamino)-1-hydroxyethyl]-2,6-dichlorocarbanilate; 4^1-[2-(tert-butylamino)-1-hydroxyethyl]-2^1,6^1-dichloroacetanilide; 5-[2(tert-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile; 4-amino-4-(benzyloxy)-N-tert-butyl-3,5-dichlorophenethylamine and the non-toxic, pharmaceutically acceptable acid addition salts thereof.

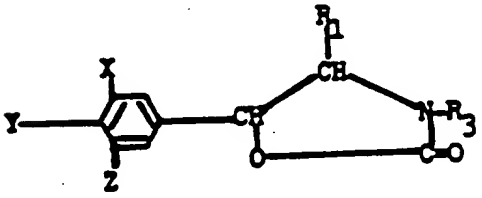
4. An animal feed supplement useful for enhancing the growth rate and lean meat deposition in warm-blooded animals comprising from about 75% to 95% by weight of a compound having formula selected from the group consisting of:



(I);



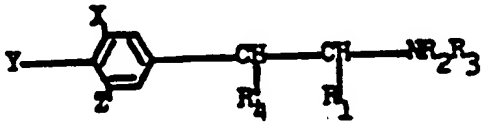
(Ia); and



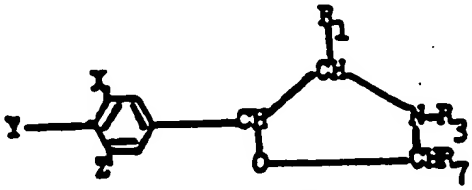
(Ib)

wherein X, Y, Z, R_1, R_2, R_3, R_4 and R_7, are as defined in claim 1 above and from about 5% to 25% by weight of a suitable carrier or diluent.

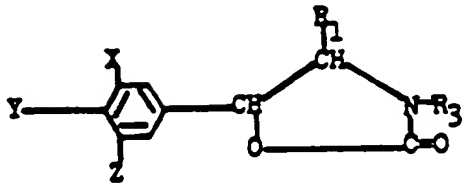
5. An injectable composition useful for enhancing the growth rate and lean meat deposition in warm-blooded animals comprising as an active ingredient a compound having a formula selected from the group consisting of:



(I);



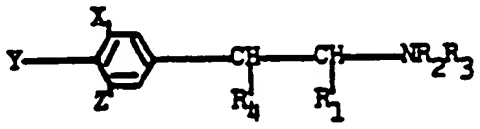
(Ia); and



(Ib)

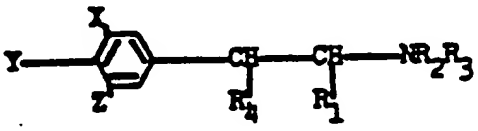
wherein X, Y, Z, R_1, R_2, R_3, R_4 and R_7, are as defined in claim 1 above, and a pharmaceutically acceptable carrier.

6. A composition according to claim 5 wherein the active ingredient is administered to warm-blooded animals in an amount sufficient to provide said animals with from 0.001 to 100 mg/kg/ day of body weight of the active ingredient having the formula:



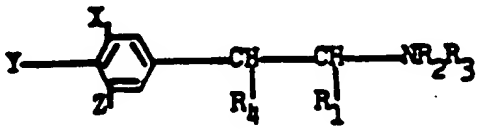
wherein X, Y, Z, R_1, R_2, R_3, and R_4, are as defined in claim 1 above.

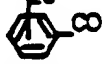
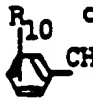
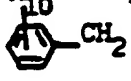
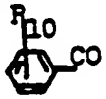
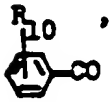
7. An implant useful for increasing the dressed carcass weight of meat-producing animals and enhancing the lean meat to fat ratio thereof comprising as the active ingredient a compound having the structure:



wherein X, Y, Z, R_1, R_2, R_3 and R_4 are as described in claim 1 above, and a pharmaceutically acceptable carrier.

8. A compound of the formula:



wherein X is hydrogen, halogen or -CN; Y is hydrogen, NR_8R_9 or $NHCOR_5$; Z is halogen, -CN, CF_3, COOR, $CONH_2$, C_1-C_4 alkyl, C_1-C_4 alkoxy, NO_2 or C_1-C_4 dialkylaminomethyl; R_1 is hydrogen or C_1-C_4 alkyl; R_2 is hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_3-C_4 alkenyl, C_2-C_5 alkanoyl or  ; R_3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_4 alkenyl, phenyl or benzyl; R_4 is OH, OR_6, or OR_{11}; R_5 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy,  or  ; R_6 is C_1-C_6 alkyl, C_2-C_5 alkanoyl,  ,  or  ; R_8 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkenyl; R_9 is hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, C_3-C_4 alkenyl or benzyl; R_{10} is hydrogen, chloro, dichloro, methyl, dimethyl, methoxy, dimethoxy or nitro; R_{11} is C_1-C_6 alkyl, phenyl, benzyl; with the provisos that when Y is NH_2, $NHCH_3$, NHC_2H_5, R_4 is OR_6 or SR_{11}; and when Y is hydrogen, X and Z are halogen, R_2 is hydrogen, C_2-C_5 alkanoyl or  and R_3 is isopropyl, 2-butyl or t-butyl; and when X is -CN, Z is -CN; and when R_6 is alkanoyl or  , R_2 and R_3 are substituents other than hydrogen, except when R_3 is an alkyl or a substituted alkyl group which contains a tertiary carton attached to nitrogen; and when R_8 is C_1-C_4 alkyl or C_3-C_4 alkenyl, R_9 is C_1-C_4 alkyl or C_3-C_4 alkenyl; and further provided that when X and Z are halogen and Y is hydrogen or NH_2 then R_4 cannot be hydrogen, OH or OR_6 where R_6 is C_1-C_6 alkyl; racemic mixtures of the above - identified compounds and the optically active isomers, and non-toxic pharmacologically acceptable acid addition salts thereof.

9. A compound according to claim 8 wherein said compound is:
N-tert-butyl-3,5-dichloro-4-methoxy-4-methylaminophenethylamine; α-[(tert-butylamino)methyl]-3,5-dichloro-4-isopropylaminobenzyl alcohol; 5-acetylanthranilonitrile; 4-amino-N-tert-butyl-3,5-dichloro-α-(methylthio)phenethylamine; α-[(tert-butylamino)methyl]-3,5-dichloro-4-dimethylaminobenzyl alcohol; 4-amino-α-(benzyloxy)-N-tert-butyl-3,5-dichlorophenethylamine; 4-(allylamino)- -[(tert-butylamino)methyl-3,5-dichlorobenzyl alcohol, and the non-toxic, pharmaceutically acceptable acid addition salts thereof.

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